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The Acute Radiation Syndrome:

A Study of Nine Cases and a Review of the Problem

By

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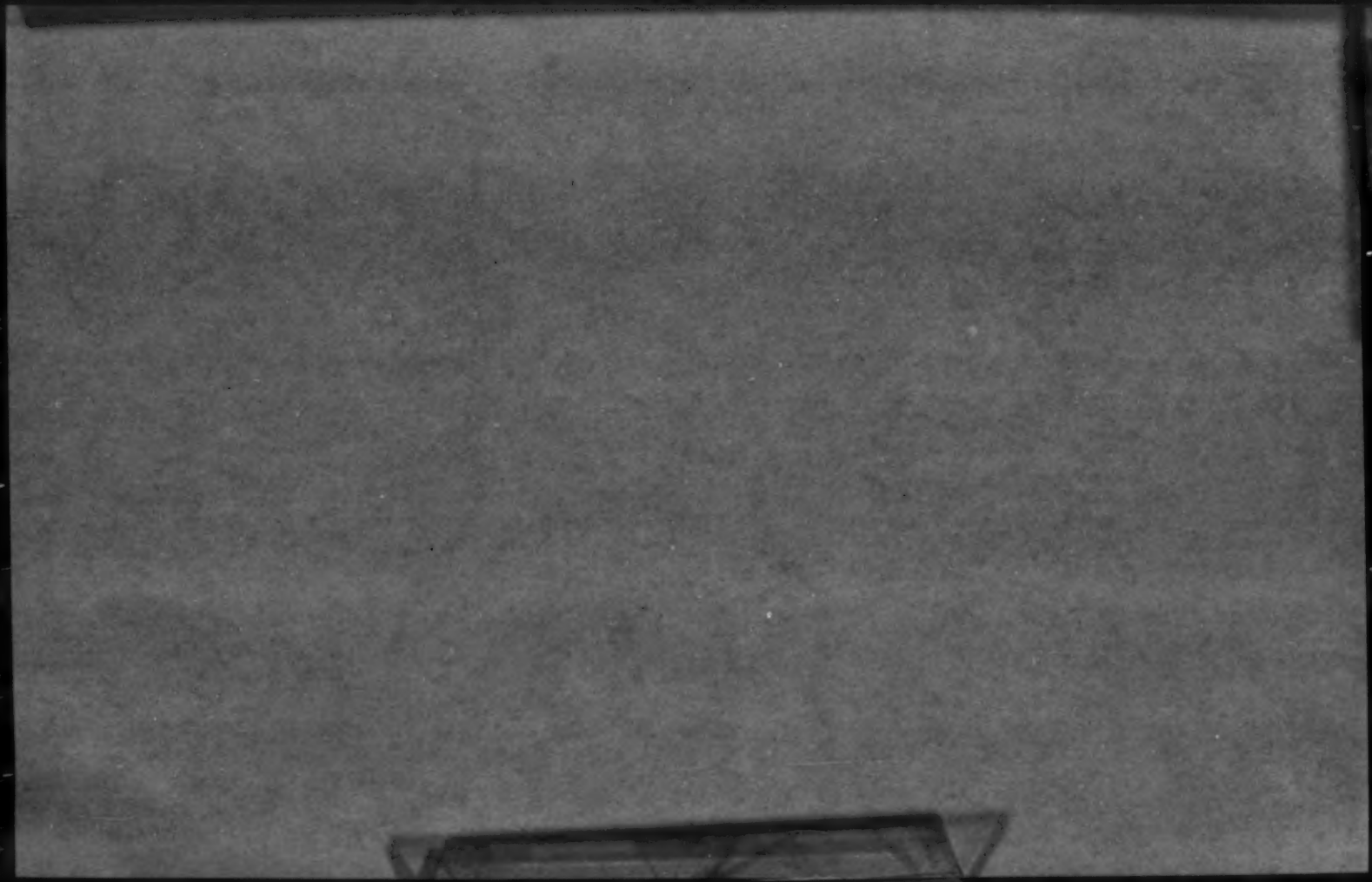

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PART 1

THE ACUTE RADIATION SYNDROME: A STUDY OF NINE CASES AND A REVIEW OF THE PROBLEM *

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Foreword

The cases of acute radiation syndrome reported in this monograph are among the few instances of such injuries that have occurred on the Atomic Energy Program since its inception. The study of the illness of these individuals and the efforts made to aid them add much to our knowledge of acute radiation injury in man. This is particularly true in those cases who were fatally injured. The story of the survivors shows that an individual can be exposed to a large dose of radiation and still return to a productive vigorous life. The data presented in this article supplement the information gained at Hiroshima and Nagasaki, particularly for the period shortly after exposure when the Japanese observations were meager. Although these injuries are of the same general type as those caused by a full scale atomic explosion, it should be emphasized that they are peculiar to a nuclear reaction on a limited scale and unaccompanied by biologically significant amounts of heat and blast.

Shields Warren.

Introduction

Acute radiation syndrome is the name applied to the group of signs and symptoms that characterize the illness produced by exposure to ionizing radiation of the entire body or a large part of the body. This illness runs an acute course lasting only a matter of weeks. The syndrome differs in this respect from the chronic form of radiation injury caused by repeated or protracted exposure of the body to radiation. Chronic injuries are manifested as gradually developing illnesses, such as aplastic anemia or leukemia. The acute radiation syndrome is also distinct from the most common type of radiation injury, i.e., that produced by irradiation of a limited part of the body. The latter is localized but, like the generalized injury, may also be either acute or chronic in nature. X-ray burns of the skin provide a well known example of acute localized radiation damage, while atrophy, hyperkeratosis and epitheliomata of the skin are characteristic forms of chronic localized injury.

Several years ago at the Los Alamos Scientific Laboratory two accidental nuclear reactions occurred which injured 10 persons. The case histories of nine of the 10 patients are presented in this report. Because there are no other examples of this type of acute radiation injury, the case histories are reported in considerable detail and the implications of the clinical and laboratory observations are discussed fully. Since these cases are unique, all pertinent data are presented in this report. Summaries are given at the end of each case history and after the discussion of the different aspects of the illness.

This report is written primarily for the clinician; therefore, emphasis has been placed on the clinical, hematologic and pathologic aspects of these illnesses. In order to give the practicing physician a better understanding of the nature of the injuries, certain basic physical phenomena are described. Also, the mechanisms by means of which ionizing radiations cause tissue damage are discussed. The illnesses of the patients presented in this study are compared with the acute radiation syndrome as it was observed in Japanese victims of the atomic explosions in 1945. An effort has been made to review the pertinent literature. The written review does not extend beyond February, 1950, but where new concepts have been proposed since then, the current views are expressed as footnotes.

Highlights of the Case Histories

Within a year of the first military use of the atomic bomb, two nuclear accidents occurred at the Los Alamos Scientific Laboratory. As a consequence of these temporarily uncontrolled fission reactions, a total of 10 persons was exposed to bursts of penetrating ionizing radiations. Two of these individuals died as a result of their radiation exposure; the remaining persons received smaller but, in most cases, clinically significant doses of total-body radiation. One of the survivors showed the typical manifestations of the acute radiation syndrome. Hematologic changes were demonstrated in this patient and in four of the six other exposed but asymptomatic persons.

The radiations responsible for the body damage in these patients were chiefly moderately fast neutrons and hard gamma rays. Heat and blast, which, alone and in combination with ionizing radiation, were responsible for so many casualties in the bombed Japanese cities, did not contribute to the injuries of these persons. The neutrons, which accounted for the bulk of the tissue damage, had limited powers of tissue penetration despite their rather high energies. Like soft x-rays, they were absorbed in each case largely in the superficial few inches of flesh nearest the experimental nuclear reactors. This means that the bodies of the exposed persons were not irradiated uniformly throughout. These radiation exposures were also unusual in that the hands and abdomen of the fatally injured individuals received an exceptionally heavy dose of radiation, in contrast to the lesser amount delivered to the rest of the body.

The complexity and uncertain quality, as well as the uneven distribution of the radiations incident on the bodies of these persons, make it difficult to express the doses in a simple manner. However, using reasonable assumptions, it has been possible to compute the doses for the hard and soft radiation components. They have been estimated in terms of the doses in roentgens of gamma rays and soft x-rays, to which the effects of this mixed radiation are believed to be equivalent. The calculated doses are presented in the form of a table on page 293, and the assumptions on which the calculations are based are presented in Sections II and X of this report.

The constitutional reaction of the two fatally injured patients followed a pattern characteristic of the acute radiation syndrome. The patients showed a prompt initial reaction (nausea, vomiting, prostration and mild fall in blood pressure) during the first postexposure day; in one case, the initial phase was present in less severe form during the second day. This was followed by a period of relative well being during which the patients had few symptoms, except for those due to the localized damage of the hand tissues. Within a week after exposure both patients went into the third, or toxic, phase of the syndrome, characterized by increasingly high fever, pronounced weight loss and prominent gastrointestinal symptoms. Despite supportive therapy, which consisted largely of the administration of whole

blood and plasma, fluids and penicillin, death occurred in one patient on the ninth post-exposure day, and in the other on the twenty-fourth day after the accident.

The clinical courses of the two fatally injured patients deviated in some respects from that usually associated with the acute radiation syndrome, or at least showed exaggeration of some of the features of this illness. In both instances, the unusual reactions, or more correctly, the unusual degree of reactions, are believed to be related to the uneven irradiation of the body as well as to the magnitude of the radiation doses. The more heavily irradiated patient, whose course was fulminating and relatively brief, showed paralytic ileus of such severity that it required continuous gastric suction. Terminally, this patient went into circulatory collapse and just before death developed jaundice and mild hemorrhagic manifestations. The other patient had a more gradually developing febrile course and showed complicated side reactions. In addition to mild diarrhea and abdominal distention, he manifested a severe stomatitis, which was biphasic in nature. He also had an attack of acute paroxysmal tachycardia (presumably an individualized response, since he had Wolff-Parkinson-White syndrome), followed by pericarditis of unknown origin. He died without showing hemorrhagic phenomena clinically.

In addition to the constitutional reactions, these patients showed extreme damage to the tissues of their heavily irradiated upper extremities, and less marked but still severe damage to the skin of their bodies. Unlike the usual delayed tissue manifestations of a local nature associated with acute exposure to radiation of a limited part of the body, the reaction of the upper extremities in both cases was almost immediate. The prompt nature of the tissue response was due to the overwhelming doses of radiation delivered to these tissues, equivalent to tens of thousands of roentgens of x-rays. Subcutaneous edema and changes in the peripheral blood flow were noted within a matter of minutes or hours. This went on to epidermolysis with blister formation within three days. In the patient who lived 24 days, epidermolysis proceeded until the skin of the hands and both forearms was lost. Some of the exposed dermal tissues showed late ischemic necrosis. In the region of the fingers, tissue necrosis progressed to the point of actual dry gangrene. This patient also showed extensive epidermolysis of the skin of the abdomen and epilation of the hair of the scalp and beard. In the other patient, who died nine days after exposure, the progression of the damage to the hand tissues was controlled by packing the upper extremities in cracked ice. The severe reaction of the abdominal skin of this patient had not reached the blistering stage at the time of death.

In the case of the survivors, only one of the persons discussed in this report developed clinical manifestations of the acute radiation syndrome. This patient showed an initial reaction, chiefly nausea and vomiting of a moderate degree. Except for a short bout of fever and prostration of several days' duration he was asymptomatic for the most part during the two-

week period of hospitalization following the accident. During the third week, he lost some of the hair of the scalp and beard; he also experienced pronounced fatigability on exertion when allowed to leave the hospital. The severity of the delayed fatigability, which lasted several months, was unexpected in this patient, who otherwise did not appear to be ill. Also, evidence of severe damage to the germinal tissues was obtained within a matter of months following exposure, but this proved to be of a temporary nature. Five years after exposure this man is in good health, although he has developed bilateral radiation cataracts, the first in the left eye three years after exposure.

The remaining six survivors showed no symptoms of any kind, even though the radiation doses of several did not differ greatly from that of one of the survivors with symptoms. All of the asymptomatic survivors were in good health, three and a half years after the accident.

The clinical laboratory findings in these persons are of considerable interest, as they throw some light on the underlying disturbances in body physiology caused by acute exposure to such large doses of total body ionizing radiation.

The blood counts showed essentially the same changes noted in the Japanese radiation casualties. Thus, pancytopenia occurred terminally in the fatally injured patients, and immediate and sustained lymphopenia was noted in most of the exposed persons. Neutropenia and thrombocytopenia of a moderate degree and temporary nature occurred only in the more heavily irradiated persons, one of whom showed a mild fall in erythrocyte count during the second postexposure month. It is interesting, however, that an initial and usually marked granulocytosis was observed in all persons, and a prompt temporary monocytosis was noted in six of the survivors. Five of the six asymptomatic survivors developed eosinophilia of probable significance. Uncoagulability of the blood was observed in one of the fatally injured patients at the time of death, and several of the survivors, who had no hemorrhagic manifestations, showed prolongation of the blood clotting time.

The studies of the chemistry of the blood did not reveal changes of a specific nature or marked degree. Significant abnormalities were observed in one of the fatally injured patients whose blood was carefully studied. There was a gradual fall in serum sodium and blood chloride, a terminal rise in blood nitrogen and uric acid and a fall in serum calcium. These changes were not of a degree sufficient in themselves to cause death of the patient. This patient, as well as one of the survivors, also showed an increase in the alpha globulin fraction of the blood protein. The studies of the urine chemistry were more enlightening. Those patients receiving the highest radiation doses excreted large amounts (up to 1 to 2 mg. per ml. urine) of urinary amino acids, particularly taurine, as well as greater than normal quantities of substances which may be corticoids. The aminoaciduria is believed to be due to a deficiency in amino acid utilization and

possibly to increased tissue breakdown, while the excretion of increased amounts of a corticoid-like substance suggests adrenal dysfunction. These patients also showed some disturbance in porphyrin and urobilinogen excretion.

One of the most interesting observations was the radioactivity of the tissues induced by the neutrons that had entered the patients' bodies. The determination of the amount of radioactivity, particularly in the serum sodium, gave the best data from which the neutron doses could be computed. The activities of the blood samples were surprisingly high, amounting to 70,620 beta particles emitted per minute from the sodium alone in 5 ml. of blood serum in the most heavily irradiated patient; the radiation from the induced radioactivity of body tissue, however, contributed little to the total body dose and did not constitute a hazard to persons with whom the patients came in contact. The radioactivity in a gold inlay in the teeth of one of the patients, however, is believed to have contributed significantly to the reaction of the adjacent tissues, and this is an exception to the general statement above.

Postmortem examination provided further information that helped to explain certain clinical manifestations in these patients. Widespread destruction was observed in the radiosensitive organs as well as in the superficial tissues which received the highest radiation doses. Although all types of cell death (including that, en masse, due to disruption of the blood supply) could be seen, cytolysis of dividing cells was the most characteristic of radiation damage. Death of cells during or shortly after mitosis was particularly conspicuous in the rapidly proliferating tissues. This type of disintegration serves to illustrate the fact that many cells fatally injured by radiation are capable of surviving until they attempt to divide. In contrast to the rather generalized destructive processes, the ductal epithelium of the sweat glands, alone among the tissues of the body, showed a marked proliferative response. This is believed to be secondary to early damage of the cells, rather than to represent a primary stimulating effect of radiation. Aside from the destructive and proliferative tissue changes, an inflammatory reaction was found in many tissues. This response was unusual only in the almost complete absence of granulocytes in the cellular exudate. Changes of a nonspecific nature were observed in certain non-radiosensitive tissues such as the liver, the adrenals and the kidneys. Tissue damage in these cases is believed to be the combined result of primary injury by radiation and secondary injury due to the flooding of the body with the products of infection and protoplasmic degradation.

Two general conclusions of utmost practical importance may be drawn from this study and from the correlation of these observations with those reported in the literature. The first conclusion is concerned with the nature or physiologic basis of the acute radiation syndrome, and the second deals with the present state of the therapy of this type of injury.

The conclusion concerning the fundamental nature of the acute radiation syndrome is that widespread destruction of tissues throughout the body is the basis for the physiologic or clinical response. The destructive processes in this disease differ somewhat from those produced by other common toxic agents which originate outside the body. In the first place, the tissue damage and destruction are not confined to the surface of the body but, in the case of the penetrating radiations, occur primarily in the radiosensitive tissues, wherever they are located in the body. In this third dimensional quality, as well as in its selectivity of organ damage, the acute radiation syndrome resembles certain chemical poisonings, e.g., benzol, more closely than other traumatic injuries, such as thermal and electrical burns and the crush injuries. A second peculiarity of the tissue destruction caused by ionizing radiation is that it is delayed rather than immediate, as is tissue death caused by thermal burns. Furthermore, the delay in the appearance of tissue damage varies from one organ system to another. The reason for the latent period before tissue damage becomes manifest is that the radiation doses usually responsible for the acute radiation syndrome tend to injure cells in such a way that many can survive until they attempt mitotic division. Since the mitotic activity is inhibited by radiation exposure, cell death does not occur until the tissue regains its ability to proliferate. If these peculiarities of tissue destruction are taken into consideration, the overall clinical or constitutional response of an individual with the acute radiation syndrome is found to be similar to that observed in other diseases in which tissue death is prominent. Thus, many features of the illness of the present patients, including secondary reactions such as infection, fluid loss and presumably the adrenal response, resemble those seen in severe thermal burns, intestinal obstruction and massive gangrene.

The conclusion regarding the state of therapy of the acute radiation syndrome is that at present one can offer only supportive therapy directed at helping the individual to survive the acute phase of the illness. Although there are a number of means by which tissues can be protected to some extent against the damaging action of penetrating radiations, there is no known method of saving doomed cells once injury has occurred.* However, there is every reason to believe that the regenerative powers of most tissues are so great that considerable, if not almost complete recovery will occur if the individual survives the critical toxic stage. In this respect, antibiotics, transfusions and maintenance of the fluid and electrolyte balance are believed to be helpful.

* See Section VI for a report of recent experiments which indicate that damage to tissue can be modified after irradiation.

SECTION I. THE NATURE OF THE RADIATION ACCIDENTS

A. Description of the Nuclear Reactions
B. Comparison of These Nuclear Reactions with an Atomic Explosion
C. Contrast of These Cases with the Japanese Casualties

I. THE NATURE OF THE RADIATION ACCIDENTS

Although large quantities of fissionable materials have been handled at the Los Alamos Scientific Laboratory during the past six years, only two serious accidents have occurred as a result of temporarily uncontrolled nuclear chain reactions. The first accident took place on August 21, 1945. Two persons were directly exposed to the ionizing radiations given off during the reaction and immediately thereafter. In the second accident, nine months later, May 21, 1946, eight persons were simultaneously exposed to radiation. All persons involved in both accidents were taken immediately to the Los Alamos Hospital for observation and treatment.

A. *Description of the Nuclear Reactions*

Both accidents were similar in nature. Each occurred during an experiment designed to test the nuclear properties of fissionable material. In conducting such studies, an experimental nuclear reactor called a "critical assembly" is used. In the course of an experiment of this type, the nuclear fission characteristics of the fissile material are determined during the systematic modification of either the mass or the geometry of the assembly. When the assembly reaches a "critical" configuration, it is in a state in which a nuclear reaction can be sustained at a certain intensity without increasing or diminishing. The number of fission neutrons created per unit time within such an assembly will just equal the number lost from the reactor by escape and by other means. If the critical size of the assembly is exceeded, a chain reaction, when started by even a single neutron, will increase exponentially; if the critical dimensions are not attained, a chain reaction will soon die out. Needless to say, the accidents occurred when the assemblies unexpectedly exceeded the critical dimensions.

When fissionable material first became available in large amounts, it was not technically possible to do critical assembly experiments by remote control in such a way that the operators would be adequately protected from the effects of a possible accidental nuclear reaction. Thus it was necessary, for about a year, to perform these experiments with operators in the immediate vicinity of the assembly, despite the dangers known to be inherent in such an operation. Stringent supervision of the experimental procedures was relied upon to prevent the assemblies from inadvertently becoming supercritical.

It should be pointed out that, under normal operating conditions, the radiations from an assembly brought to critical dimensions were of low

intensity in the working areas. The daily radiation exposures of the operators normally averged much less than 0.01 rem.

B. *Comparison of These Nuclear Reactions with An Atomic Explosion*

It is natural to compare the nuclear reactions in these assemblies with those that occur when an atomic bomb is detonated, and to contrast the injuries resulting from these accidents with those injuries produced by the atomic explosions in Japan. The sequence of nuclear fission reactions in a supercritical reactor and in an exploding atomic bomb is identical. The primary difference in the two cases lies in the amount of nuclear energy released and in the distance of the event from the individual concerned. In an atomic explosion, a large amount of nuclear energy is transformed into mechanical energy, heat and ionizing radiation, any one of which is sufficiently intense to cause injury or death to persons within a large area. In the Los Alamos assemblies which exceeded critical dimensions, the nuclear reactions proceeded to a point where ionizing radiations were the sole type of energy that produced biologic damage, and these radiations were injurious over only a limited range. Thus, the injuries reported in this paper were due to the action of radiation alone, while those in Japan were due to the combined effects of blast, heat and ionizing radiation. Most persons in the center of the bombed area of the Japanese cities were subjected to at least two of these damaging physical agents. Cases of pure radiation injury, uncomplicated by blast effects (direct and indirect) and flash burns, could be found only at the edge of the bombed areas. They constituted about 5 to 15 per cent of the total bombing casualties.

C. *Contrast of These Cases with the Japanese Casualties*

The cases presented in this article are similar in character to the uncomplicated acute radiation injuries observed in Japan. The biologic damage in both instances resulted from the brief exposure of the entire body of an individual to ionizing radiation. In both circumstances, the radiation entered the body through the surface closest to the nuclear reaction.

Certain points of dissimilarity between the composition and energy of the incident radiation and the absorption of the radiation in the bodies of the exposed persons must be kept in mind when the injuries at Los Alamos are compared with those in Japan. These differences are largely the result of the inequality of radiation absorption in the medium through which the radiation passed before reaching the individuals. In the case of the Japanese explosions, the radiation traversed several thousand yards of moisture-laden air. In the Los Alamos accidents, in contrast, the radiation had a short course in shielding materials and a negligible pathway in air. The absorption of radiation by the large mass of air in the former situation was much greater than that by the comparatively small amount of shielding material around the critical assemblies. Therefore, the incident radiation

in the Los Alamos cases was less heavily filtered than that which caused the Japanese injuries. This means that the radiation that caused the bodily damage in the present series of cases had a higher neutron-to-gamma ray ratio than that which caused the Japanese injuries. Furthermore, the damaging electromagnetic radiations were less energetic than those in Japan and had, in addition, a sizable component of very soft rays, as will be pointed out later.

The vast difference in distance between the reaction and the exposed persons in the two situations also contributed to dissimilarities of dosage distribution, as did the uneven shielding of the Los Alamos assemblies. The radiation dose, in the case of the Japanese, was usually uniformly distributed throughout the bodies. Although the radiation delivered to most of the present cases was also uniformly distributed over the body surface, that which caused the injury of cases 1, 3 and 4 was uneven in distribution as will be brought out later. The severely damaged upper extremities of cases 1 and 3 had no counterpart in the Japanese victims of the atomic explosions.

It should be emphasized that in neither Japan nor Los Alamos was there contamination of the injured persons with radioactive fragments of the atoms that had undergone fission.

SECTION II. RADIATION DOSES

A. Character of the Radiations Resulting from Nuclear Reactions
B. Nature of the Radiation Reaching the Bodies of the Operators
C. Radiation Dose Calculations
D. Further Considerations of Characteristics of the Calculated Doses

II. RADIATION DOSES

The dose of radiation delivered by an x-ray tube of known characteristics can be determined by a single measurement with an appropriate instrument. The radiations from these nuclear assemblies, however, were so complex that physical measurements made at the time of the accidents could not be converted directly into dose units. It was not until these radiations had been characterized by theoretical and preliminary experimental study that calculations of the radiation doses received by the operators could be undertaken. Even at the present time, some properties of the radiation are not known; this uncertainty is reflected in the calculated doses.

Before the radiation dose delivered to the operators can be considered, it is necessary to discuss the character of the complex radiations given off by the nuclear reactors, and to mention the attenuation and scattering of the radiations escaping from the critical assemblies.

A. *Character of the Radiations Resulting from Nuclear Reactions*

The ionizing radiations emitted during and shortly after the nuclear reactions were neutrons and gamma and beta rays. Following the cessation of the fission reactions, gamma and beta radiations were given off by the radioactive fission fragments. Absorption of the beta rays by the material comprising the assembly gave rise to x-rays of moderately low energy. Both moderately high-energy neutrons and hard gamma rays escaped from the enclosed assemblies in numbers sufficient to cause serious body injury. The beta radiation and x-rays were largely absorbed within the critical assembly and surrounding shielding materials. It is certain, however, that enough very soft radiation of this type escaped to contribute significantly to the hand damage and possibly to the skin damage of the bodies of the two fatal cases.

As indicated in the previous section, the time of reaction, and therefore the period of radiation exposure, was short, and there was no contamination of the exposed persons by radioactive fission products deposited either within or on their bodies.

B. *Nature of the Radiation Reaching the Bodies of the Operators*

A brief consideration of the complexity of the radiations reaching the bodies of the operators serves to illustrate the difficulties encountered in computing the radiation doses.

The penetrating radiations resulting from atomic fission were tempered by partial absorption within the fissionable material itself and in surrounding structures. The radiations escaping from the assembly were further modified by being scattered from the shielding materials, as well as from the floor and walls of the laboratory. Thus the radiation that reached the bodies of the individuals was a complex mixture of primary and scattered rays of varying energies and intensities. The actual energies of the incident radiation, subjected to these various modifying influences, are known only within broad limits, but it is certain that the mean energy of the gamma rays was high, while that of the neutrons was considerably lower. The gamma rays may be considered to be hard, while the neutrons were only moderately fast. In addition to these penetrating radiations, there was an unknown but large amount of beta rays and very soft secondary x-rays.

To complicate the picture further, the incident radiation mixture was not uniformly distributed over the body of some of the individuals. The unevenness of the exposure was largely a consequence of the fact that the radiation flux close to the assembly was nonhomogeneous, due in part to the way in which the shielding was constructed. This allowed certain parts of the body to be in regions of very high radiation intensity while the remainder of the body was in the shadow cast by relatively more effective shielding materials.

C. *Radiation Dose Calculations*

When information about the characteristics of the radiations became available, it was possible to use physical data obtained during the accidents to compute the total radiation doses received by the 10 operators. Of the measurements made during the nuclear reactions (photographic film blackening, radioactivity in elements that capture neutrons and other data), perhaps the most valuable was that gained from the study of the radioactivity of the body tissues. (See Section VIII.) Since the ratio of neutrons to gamma rays in the fission process is known, the measurements of the neutron-induced radioactivity of the tissues give data from which the total quantity of penetrating radiation absorbed by the entire body may be computed.

The values for the radiation doses were determined by calculating independently the gamma ray and neutron doses in terms of megagram roentgens. (See Section IV-A.) These two doses were then combined to obtain the total radiation dose. The effect of gamma rays on tissue depends upon a well understood interaction of the incident radiation with electrons of tissue atoms. The gamma ray dose, therefore, is derived by a straightforward calculation in which the uncertainty of the average gamma ray energy is the only source of error, and even this error involves but minor corrections. The biologic action of neutrons, on the other hand, is dependent upon (*a*) collisions of these particles with the nuclei of light tissue elements, mainly hydrogen; (*b*) gamma rays emitted by the atomic nuclei, also chiefly hydrogen, which finally capture the slowed down neutrons; (*c*) other nuclear reactions. (See Section VIII.) These interactions are much more complicated and less well understood than is the absorption of gamma rays. This means that there are possibilities for error in the neutron dose computation besides that due to the uncertain quality of the incident neutrons. Nevertheless, it seems clear that the uncertainty in the degree of modification of the energy of the incident neutrons is the most important single unknown factor in the radiation dose calculations.

TABLE I

Radiation Doses in Terms of Energy Absorption

Case	Heavy Particle Dose* (Proton Recoil and Emission) (megagram-roentgens)	Capture-Gamma Dose (Neutron Capture) (megagram-roentgens)	Prompt-Gamma Dose (Fission Burst) (megagram-roentgens)	Delayed-Gamma Dose (Fission Fragments) (megagram-roentgens)	Total Dose (megagram-roentgens)
1	2.00	1.41	—	5.0	8.41
2	0.12	0.008	—		0.128
3	5.23	3.59	0.68		9.50
4	1.40	0.96	0.36		2.72
6	0.58	0.39	0.07		1.04
7	0.51	0.34	0.09		0.94
8	0.18	0.125	0.08		0.305
9	0.15	0.098	0.034		0.282
10	0.09	0.06	0.03		0.15

* Relative biological effectiveness of moderately fast neutrons not considered.

TABLE II

Best Estimate of Radiation Dose in Terms of γ-Rays and Soft X-Ray Equivalent*

Case	Whole Body**		Hands***	
	80-Kv X-Ray Dose Equivalent (roentgens)	γ-Ray Dose (roentgens)	Right Soft X-Ray Equivalent (roentgens)	Left Soft X-Ray Equivalent (roentgens)
1	480	110	20,000–40,000	5,000–15,000
2	31	0.14		
3	1930	114	3,000–10,000	15,000–30,000
4	390	26.4		400–600
6	186	10.7		
7	140	8.7		
8	55	4.37		
9	42	2.72		
10	33	2.41		

* Delivered as a plane wave from a source at infinity.

** Not including very-soft secondary radiation; average gram-roentgen per incident roentgen is 0.21; R.B.E. taken as 5.

*** Estimate in terms of soft x-rays, including secondary radiation; R.B.E. factor taken as 5.

The calculated radiation dose received by each operator is listed in tables 1 and 2. These values have been taken from a report by one of the authors (Hoffman, 1947). Table 1 gives the breakdown of the radiation doses into their gamma ray and neutron components on the basis of the energy delivered by each to the tissues. The megagram-roentgen, the dose unit used in this table, is defined in Section IV-A. The first column of table 1 indicates the energy that is lost by the fast neutrons as a result of being slowed down in the tissues by collisions with the light atomic nuclei and by nuclear reactions with tissue nitrogen involving proton emission. The second column gives the radiation dose due to hard gamma rays emitted by the tissue atoms upon capture of the slow neutrons. The third and fourth columns list the radiation doses due to the gamma rays emitted in the first instance during the fission burst and in the second by the resultant radioactive fission fragments. It is clear from this table that most of the energy dissipated in the bodies of the exposed operators has come from the interaction of tissues and neutrons. Thus, well over 75 per cent of the dose of penetrating radiation in all cases except case 1 is accounted for by the values given in columns 1 and 2.

It must be emphasized that table 1, which gives the basic data for all dosage considerations, may be misinterpreted unless certain facts are kept clearly in mind. In the first place, the great efficiency of neutrons in causing tissue damage is not taken into account in these physical data. When this biologic factor, the so-called relative biologic effectiveness (the R.B.E., more fully discussed in Section IV-A), is taken into consideration, the values in column 1 are raised by a factor of at least four or five. Secondly, the neutron dose, presented in column 1 in terms of the total energy dissipated in the entire body divided by body weight, is expressed as if the neutron

recoil energy were uniformly absorbed throughout the body. This is not true, since the path in tissue of neutrons of this energy is short, and therefore the energy from neutron collisions was absorbed largely in the superficial few inches of tissue. Thus the neutron recoil dose was limited to the surface tissues, rather than distributed equally throughout the body. This short neutron path, which concentrates energy loss in the superficial tissues, increased the damage done by neutrons in these tissues. Thirdly, the high total neutron dose, which can be obtained by adding the values in columns 1 and 2 in table 1, must not be interpreted as indicating that the radiation mixture given off during the nuclear reaction was composed predominantly of neutrons. Rather, it signifies that the incident neutrons, due to their limited range in tissue, were almost completely absorbed by the tissues, while the more penetrating gamma rays lost only a fraction of their total energy as they passed through the bodies of the operators.

Table 2 attempts to take into account the biologic considerations just mentioned, and gives the doses in terms of the biologic equivalents of their low-penetrating and high-penetrating components. It is consistent with the physical facts, so far as the depth dose distribution is concerned, to think of neutron recoil dose as resembling that of soft x-rays, provided the relative effectiveness of the two types of radiation is taken into consideration. It must be realized, however, that this method of presentation is, at best, only an approximation, since the R.B.E. is not constant for different tissues or various biologic effects, and the distribution of tissue dose in the case of moderately fast neutrons is not identical with that of soft x-rays. Nevertheless, an R.B.E. (between neutrons and x-rays) of 5 was used in these calculations, and 80-kilovolt unfiltered x-rays were chosen to approximate the depth dose distribution in the body produced by the neutrons in question. The value of the R.B.E. was taken from comparisons of the acute lethal actions of neutrons and gamma rays on animals, and is undoubtedly low for many biologic effects, particularly those of a delayed nature. Despite these limitations, inherent in attempting to simplify doses of complex radiation by converting them into equivalent roentgens of gamma rays and soft x-rays, it seems worthwhile to present the physical data in this manner in order to facilitate comparison with previous clinical and experimental data on exposure of the whole body to radiation.

Since expression of these radiation doses in this manner involves the assumptions just discussed, it has been suggested that the actual doses can best be considered in terms of the specific activity of the sodium in the blood serum of the irradiated subjects. These values, presented in table 3, refer to the amount of radioactivity per milligram of serum sodium. The specific activity of serum sodium is an index of the number of neutrons absorbed in the whole body, and has been used here as the basis for the calculation of the neutron doses given in table 1. (See also Section VIII.) As the neutron dose in these accidents constitutes 80 to 90 per cent of the total dose when the R.B.E. is taken into account, the specific activity of the serum sodium

TABLE III

Specific Activity of Serum Sodium Corrected for Decay

Case	Disintegrations per second per milligram sodium
1	18.0
2	1.1
3	73.6
4	13.3
6	7.1
7	3.8
8	2.03
9	1.54
10	1.22

may be considered to give a good approximation of the total body dose delivered by penetrating radiations. It is dependent, to some extent, upon neutron energy, but corrections due to this variation are probably not so great as the errors introduced by converting the data into conventional dose units. It should be remembered, however, that in considering the radiation dose in terms of the sodium specific activity, account must be taken of the amount and location of the exposed tissue. Thus, the induced activity due to exposure of a single limb, such as the forearm, should not be confused with that due to whole body irradiation. If these limitations are kept in mind, however, it seems true that the specific activity of the serum sodium, a measurable value not subject to the uncertainties of dose computation and the difficulties of expression in conventional terms, may be used as a convenient arbitrary unit in comparing relative doses in radiation exposures of this type.

D. *Further Consideration of the Characteristics of the Calculated Doses*

It is important to stress certain other features of the calculated doses. In the first place, the hand doses, unlike the body doses, are not substantiated by good physical measurements; instead, they are based on an estimation of the length of time during which the hands remained in a region of known radiation flux. The possibility of error in making such a guess must be kept in mind when the response of the hands is considered. Secondly, the fatal doses quoted for cases 1 and 3 do not take into account the unknown quantity of very soft secondary radiation delivered to the upper extremities. This type of radiation undoubtedly was responsible for a significant part of the reaction of the hands and forearms. Thirdly, in cases 1, 3 and 4, where the radiation dose was non-uniform, the values represent the *average* dose delivered to the entire body. As will become evident when the case histories are presented, the midsection of the torso of cases 1 and 3 undoubtedly received much more than the average dose listed in tables 1 and 2, while the legs and head received a smaller dose. Fourthly, it is important to realize that, although the absolute doses of the 10 operators may be questioned, the doses relative to one another, particularly as is indicated by the specific activity of the serum sodium, are probably quite accurate. The relative doses, therefore, may be used with confidence when the reactions of the different operators are compared.

Section III. Presentation of the Cases

Case 1
Clinical History
Medical Findings on Admission to Hospital
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Hematology
Pathology (see gross protocol, Appendix I-A)
Summary
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Clinical History
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Hematology
Summary

Case 1

Clinical History

This 26 year old unmarried man was brought to the hospital 25 minutes after the first accident. He was touching the experimental critical assembly when the chain reaction took place. The radiation delivered to his body was not uniformly distributed. His hands received a very large dose of radiation, the right more than the left, and the abdominal dose was greater than that delivered to the rest of the body. It is impossible to estimate accurately the radiation dose received by the hands and arms, but it seems likely that the right hand received between 20,000 and 40,000 rem (roentgen equivalent man) of soft radiation,* while his left hand received 5,000 to 15,000 rem. The dose delivered to the body (exclusive of the very-soft radiation to his upper extremities) has been calculated to be equivalent to 480 roentgens of 80-kv x-rays and 110 roentgens of gamma rays.

The past history was unusual in that the patient was known to have a cardiac abnormality, first discovered three years before, and subsequently diagnosed as Wolff-Parkinson-White syndrome. He had experienced one attack of paroxysmal tachy-

* A rem or roentgen equivalent man is a dose unit applied to radiations other than x-rays or gamma rays. One rem is defined as that amount of radiation which produces the same biologic effect as one roentgen of hard x-rays. See Section IV for further discussion of this and other dose units.

cardia of short duration but had suffered no other cardiac symptoms. His blood pressure had always been normal (120/80 mm. Hg), and his heart was not enlarged to percussion or in chest roentgenograms. Although the patient had worked with various types of radiation-producing physical equipment, his exposure to external radiation was irregular and not excessive. His daily exposure was known to have averaged less than 0.01 rem (roentgen equivalent man) of neutrons and gamma rays. Blood counts and urinalyses had been normal.

Medical Findings on Admission to Hospital

The patient was a heavy-set, moderately obese young man in good physical condition. His only subjective complaint on admission to the hospital was numbness and tingling of both hands. The oral temperature was 99° F.; respiratory rate, 20 per minute; pulse rate, 68 per minute; blood pressure, 120/70 mm. Hg. The skin of the forearms, neck and face was reddened as a result of sunburn two days before. Examination of the heart and other organ systems indicated no abnormalities. The significant physical findings on admission to the hospital were limited to the hands. The right hand was diffusely and tensely swollen. The skin of this hand was pallid but warm. There was some swelling of the index finger and thumb of the left hand, with a suggestion of redness of the grasping surfaces of the terminal phalanges of these fingers.

Course

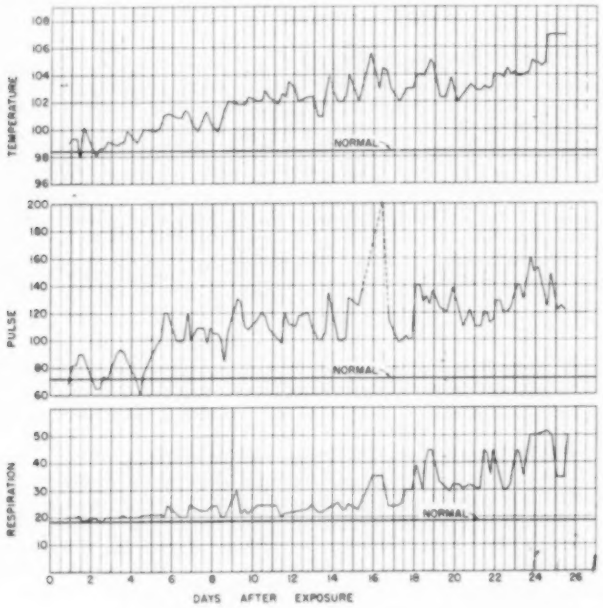
The story of the illness of this patient is very complicated. It can be described most clearly by considering the general condition and then the reaction of the individual organ systems, rather than by describing the chronologic events of the illness as a whole.

General Condition: After an initial 24-hour period of gastric distress and prostration, the general condition of the patient improved, although he continued to be very weak. Numbness in both hands was replaced by gradually increasing pain, which became the outstanding symptom during the first week. The patient had a slight irregular fever from the time of admission to the hospital. On the fifth day there was a rise in temperature associated with tachycardia. The fever became progressively higher until it exceeded 106° F. rectally on the twenty-fourth day. In the course of the illness, the patient's condition deteriorated steadily. He lost a great deal of weight and his appearance changed markedly. There were occasional periods of mental confusion during the early stages of the illness. The sensorium remained alert and morale was excellent until several days before death, when the patient became irrational. He became comatose on the twenty-fourth day and died on the afternoon of this day.

Extremities: Right Arm (Plates I to IX *): Brawny edema of the right hand was observed within 30 minutes of exposure. The swelling increased rapidly during the first day and gradually extended up the extremity to involve the forearm and upper arm almost to the axilla on the seventh day. About 36 hours after the accident, a small blister was noted on the volar surface of the third finger of the right hand. The nailbeds of all fingers had become cyanotic by this time and the skin, of the hand which had been warm, was cool to the touch. The blister increased in size throughout the day (Plate I), and within 24 hours other bullae developed on the palmar and dorsal surfaces and on the interphalangeal surfaces of the fingers (Plate II). These blisters grew larger in a matter of hours; they varied considerably in size and all were tightly distended with fluid. The largest bulla, that in the palm, measured 5 by 5 by 3 cm. (Plate III). Skin sensation of the hand gradually diminished and was absent after the third day. There was intense cyanosis of the skin of the hand on the

* Plates I through XXIV are in color and may be found at the end of this monograph.

fourth day after exposure. Initially, the patient complained of numbness of this hand. Beginning on the second day, the hand became painful. The pain increased in intensity over a period of several days and persisted for about two weeks. Codeine and morphine relieved the pain incompletely. Initial local treatment of the acute burns consisted of chilling the hands with ice bags.



Case 1.

On the third day it was decided to open the blisters, which by their very bulk seemed to be causing pain and possibly interfering with the circulation. Under general anesthesia, the dead skin was removed and absorbent pressure dressings were applied after covering the raw surfaces with vasoline gauze. The blister fluid was intensely yellow and jelled promptly on standing. Subsequent to the opening of the blisters, there was progressive extension of the epidermolysis. By the ninth day, all of the necrotic skin of the fingers (Plates IV and V) as well as the nails could be stripped off with ease. The epidermis of the entire flexor surface of the forearm and cubital fossa was lost by the third week. The dorsal surface of the forearm was not so extensively affected. Here, the process involved the skin halfway to the elbow. The desquamation appeared to become more superficial as it progressed proximally up the arm. The raw surface of the right hand, which was exquisitely tender and painful during the first two weeks, exuded large quantities of yellow fluid (Plates VI and VII). Gradually the hand ceased to weep, and during the second week of the illness the tissues began to assume the appearance of dry gangrene. By the third week, the fingers had become quite dry and black (Plates VIII and IX). The fingers could not easily be straightened, even passively when the patient was under general anesthesia. At this time there was less swelling of the upper arm. During the third

week the viable tissues of the hand were covered with a moderate amount of serofibrinous exudate and the superficial dermis showed a patchy ischemic type of necrosis.

Left Arm (Plates I, II, III, X through XIV): The initial examination of the left hand revealed some swelling of the index finger and thumb, with slight redness of the grasping surfaces. The edema of the left hand and arm gradually became more severe but was never so marked or so extensive as that of the right arm. A mild erythema of the skin of the hand and of the distal portion of the forearm was observed on the third day. The skin at the base of the thumbnail had assumed a mottled cyanotic appearance by the fifth day. During the second week, the swelling of the arm and hand diminished somewhat and the erythema faded slightly, but the cyanosis of the thumbnail persisted (Plate X). The skin reaction which was limited to the hand and wrist was most marked on the volar surfaces. There was a rather distinct line of demarcation separating the erythematous from the normal-appearing skin. On the eleventh day the patient complained of a sensation of tightness and dryness in the skin of the hand. A mixture of zinc oxide and vaseline ointment was smeared on the skin and a light dressing was applied. On the thirteenth day, when the bandage was removed, it was observed that the reddened portion of the skin had become the site of a large blister involving the entire palm, part of the dorsal surface of the hand, the entire thumb and the flexor surface of the wrist. This blister was more extensive than those of the right hand; in contrast to them, however, it was only partially distended with fluid. The dead skin was removed under general anesthesia on the fifteenth day (Plates X and XII). The underlying tissue appeared healthy except in the region of the thumb, where dry gangrene was already evident. The desquamation of the epidermis gradually progressed until almost all the skin of the dorsum of the forearm and hand was lost. The deeper tissues did not become gangrenous except in the region of the thumb.

Skin of the Torso and Face (Plates XV to XVIII): Erythema of the skin of the torso and face was first evident on the third day of the illness. It was most noticeable in the exposed parts of the neck and face which had been sunburned previously. The protection afforded by a light cotton shirt worn at the time of the accident was readily apparent. The erythema of the body slowly increased in intensity, became duskier in hue, and during the second week developed a sharp, irregular edge. Blebs appeared in the superficial layers of the skin of the torso on the seventeenth day. The groins showed the earliest and the most extensive desquamation. The raw surfaces in this region became macerated and thereafter were exceedingly tender. By the twentieth day, the denuded areas of the abdomen and of the left side of the chest had become confluent, presenting a picture of a third degree burn (Plate XVIII). During the last few days of the illness, the margins of the skin adjacent to the burned area became speckled with brown perifollicular spots.

The skin of the face and neck peeled on the nineteenth day. The reaction was superficial and not exudative. Considerable pigmentation was lost and the skin of the face assumed a pallid color and appeared tightly stretched over the bones of the face (Plate XVII). The patient had a rather prominent pigmented naevus on his right cheek which was thought to have decreased slightly in size by the third week, although no accurate measurements were made. No spontaneous hemorrhages or icterus were observed throughout the illness.

Eyes: On the fourteenth day the conjunctivae became reddened and the patient complained of burning and tearing. This condition persisted for several days.

Hair: Loss of hair in the region of the right temple was first observed on the seventeenth day. Epilation progressed for several days until both temples and the frontal portion of the scalp were almost completely bald (Plate XVII). Loss of the beard did not occur until the nineteenth day. Although there appeared to be no spontaneous loss of the eyebrows, the individual hairs could be pulled out with ease.

The body and pubic hair was shed to a great extent as the epidermis of these regions was desquamated. There was incomplete loss of axillary hair.

Gastrointestinal Tract: During the first 24 hours after the accident the outstanding complaint was severe gastric distress, manifested by nausea and repeated episodes of retching and vomiting, beginning one and one-half hours after exposure. At times the patient retched and vomited almost continuously. During the second day, the nausea persisted but the patient no longer vomited. He suffered from prolonged periods of hiccoughing during this day. There was no diarrhea or abdominal distention. Following this 48 hour period, the patient's appetite improved and he ate well.

On the tenth day, he complained of a "canker sore" on his tongue. He became nauseated on this day after eating and experienced cramping, generalized abdominal pain. Examination of the abdomen revealed moderate distention and tenderness to deep palpation, most marked in the right upper quadrant. Peristaltic sounds were prominent. The abdominal cramps were not relieved by enemata or rectal tubes. The abdominal distention became more severe and persisted for several days, after which it disappeared completely. By the twelfth day, the mucous membrane of the mouth had become the site of a generalized inflammatory reaction (Plate XVI). A gray-white transparent pseudomembrane covered almost the entire oral mucosa. This membrane was quite thick and white on the edges of the tongue, in the floor of the mouth and in the region of the buccal mucosa adjacent to the line of closure of the teeth. The hard and soft palates and posterior pharynx were not so seriously involved. There was slight bleeding from the swollen, cracked lips. The mouth became extremely sore and the patient refused food and drink. He complained of dryness and of thick mucus in his throat which caused him to gag and to vomit on the seventeenth day. It was necessary to give fluids parenterally for several days.

The reaction of the mucous membranes subsided gradually, and on the eighteenth day there were only discrete patches of the white membrane covering small ulcerated lesions on the floor of the mouth and in the buccal mucosa. There was concomitant return of the appetite as the mouth lesions healed. The improvement in the buccal mucous membranes, however, was temporary. In the terminal days of the illness, the mucosa assumed a beefy red appearance and a large ulcer with a ragged necrotic base appeared in the right cheek. The food and fluid intake remained good, however, until the day before death.

The patient passed a soft, liquid stool on the twelfth day. The stools from this day until death were soft, poorly formed and frequent.

Cardiorespiratory System: During the first few days of the patient's illness it was noted that he was dyspneic on slight exertion, such as on sitting up in bed. The blood pressure fell during the first 24 hours from 120/70 to 100/60 mm. Hg, but then returned to normal on the second day. On the fifteenth day, shortly after receiving a blood transfusion and intravenous fluid, the patient became apprehensive and complained of substernal oppression. He became pale and his skin felt cold and clammy despite a rectal temperature of 105°F. His respirations were rapid and shallow, and his blood pressure fell to 70/50 mm. Hg. Examination of the heart revealed a pronounced tachycardia (250 beats per minute) which was shown by electrocardiography to be supraventricular in origin. Repeated attempts at vagal stimulation (carotid and eyeball pressure, induction of vomiting and quinidine orally) failed to cause prompt reversion to normal rhythm. Twenty-four hours after onset, the tachycardia ceased abruptly and the heart assumed a more normal rate (110 per minute). A gallop rhythm was heard over the left border of the sternum at this time, and the heart was found to be enlarged to percussion. Electrocardiographic tracings indicated nodal rhythm. On the following day (the sixteenth day after exposure), a to-and-fro friction rub was heard over the apex of the heart, which at this time

Laboratory Data—Case 1

Urinalysis

Days After Exposure	Specific Gravity	Albumin	Bile	Acetone	Microscopic
2	1.023	0	—	—	no cells or casts
10	1.019	faint trace	—	—	occ. WBC, urate crystals
18	1.023	trace	—	—	4 WBC/HPF, occ. RBC, ++ urate crystals
21	1.016	0	—	—	1–2 WBC/HPF, occ. RBC, +++ urate crystals
24	1.018	0	trace	0	urobilinogen positive in 1:100 dilution

Gross urine specimens during last two weeks of illness showed a heavy pink sediment.

Stool Examination

Days After Exposure	Guaiac	Mucus	Microscopic
4	0	0	negative
10	+	0	negative
12	++	0	negative
16	trace	0	negative
21	0	0	undigested food particles

Blood Chemistry

Days After Exposure	Non-Protein Nitrogen mg. %	Uric Acid mg. %
14	38	2.7

Sedimentation Rate

Days After Exposure	Rate
10	16 mm. per hour

Urine Chemistry

Days After Exposure	Corticoid-Like Fraction Ratios			Coproporphyrin	
	a 220/240 mμ	b 240/260 mμ	a/b	μg. %	μg./day
24	1.45	3.6	0.40	21	252
Normal Range	1.5–1.7	0.9–1.1	1.4–1.8	4–9	30–100

Urine Amino Acids*

Day of Illness	Cysteic Acid	Aspartic Acid	Glutamic Acid	Glycine	Taurine	Alanine	Valine	Leucine	Unknown Below Alanine	Unknown Below Valine	Other
24	0.5	0.5	1.0	1.5	3.0	trace	0	0	0	0	1.5 hydroxyproline
Controls 3 cases 8–24 hrs.	0	0	0	0.1–0.25	trace	trace–0.1	trace	trace	0	0	serine—trace alanine—trace arginine—trace—0.1

* Amounts expressed in mg./ml. (approximate concentration).

LABORATORY DATA—CASE 1—*Continued*

Neutron-Induced Radioactivity of Serum and Urine

Na^{24} Activity in Serum

Sample	Time Taken (hours after exposure)	c.c. Plated	mg. P Plated	Na^{24} cpm. @ t = 0	Na^{24} Corr.* dps.	Na^{24} Corr.* dps./mg. Na	P^{32} dps./mg. P t = 0
Serum I	17.4	5	16.8**	900	300	18	bkg.

P^{32} Activity in Urine

Sample	Time Taken (hours after exposure)	c.c. Plated	mg. P Plated	P^{32} cpm. @ t = 0	P^{32} Corr.* dps. @ t = 0	P^{32} Corr.* dps./mg. P
Urine I	17.4	25	5.3	1800	600	110

Na^{24} Activity in Urine

Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm. @ t = 0	Na^{24} Corr.* dps. @ t = 0	Na^{24} Corr.* dps./mg. Na
Urine I	17.4	3.00**	25	75	5100	1700	22.5

* Corrected for counter efficiency of 0.15.
** Inert sodium not determined chemically but assumed from tables of normal values.

Neutron Induced Radioactivity of Body Tissue

Beta radiation from teeth, 12 days after exposure—*bkg.*—on portable Geiger unit.

reached the left nipple line. The friction rub disappeared on the twenty-second day of the illness but the cardiac enlargement, as determined by percussion, persisted until death. The rate of the heart increased gradually but the rhythm reverted to the normal sinus type. The blood pressure remained low (100/60 mm. Hg) from the time of recovery from the tachycardia until death.

The breathing became more shallow, slightly irregular and more rapid during the last two days of life and, on the day of death, the patient's lips were moderately cyanotic.

Genitourinary Tract: The kidney function appeared to be unimpaired throughout the illness. The output of urine never fell below 1,500 c.c. per day, even in the terminal stages of the illness. There was no evidence of significant kidney damage. A definite decrease in the size of the testes was observed on the nineteenth day.

Therapy

Attempts at therapy were limited to symptomatic procedures. Initial treatment of the injured hands consisted of chilling them by means of ice packs. A paravertebral block on the right side was performed on the third day in an attempt to improve the circulation of the cyanotic fingers. Following this, the burns on the hand were treated as thermal burns with surgical débridement and pressure dressings. The hands were redressed every three or four days and the wounds débrided so that progress of the lesions could be observed. Quinidine sulfate, 0.4 gm. very four hours, was given orally for one week after the onset of the tachycardia. Intramuscular injections of penicillin, 25,000 units, were given every three hours after the sixth day. Codeine and morphine were administered for pain as needed. The patient was placed on a nutritious bland diet with supplementary vitamins, including 30 mg. of thiamin chloride intramuscularly per day. The daily intake of fluid was kept above 3,000 c.c.

During the periods of gastrointestinal distress, and terminally, it was necessary to give fluids parenterally. Two pints of blood were administered on the fourteenth and fifteenth days. Transfusions and other types of intravenous therapy were not employed thereafter because of the patient's cardiac irregularity and his poor superficial veins. The veins in the antecubital fossa could not be used because of the tissue reaction on this region. The ankle and foot veins were small and almost impossible to cannulate, particularly in the terminal stages of the illness.

Hematology

Blood counts previous to the accident had always been normal. The preëxposure total leukocyte counts varied between 6,100 and 9,200 cells per $mm.^3$; the differential blood picture was normal.

Blood counts were made twice daily after the accident. The quantitative changes in the formed elements of the blood are shown in the accompanying graphs (p. 304) and in Appendix III. The main changes in the leukocyte count consisted of (1) two periods of granulocytosis, one lasting from the time of the accident to the seventh day, the other from the fifteenth to the eighteenth day; (2) a prompt and persistent lymphopenia, and (3) terminal and pronounced fall of all leukocyte types. The platelet count fell moderately during the period between the two waves of granulocytosis and again before death. There was a gradual fall in the red blood cell count and hemoglobin. The reticulocyte count did not change significantly. The progressive increase in abnormal lymphocytes refers to cells containing more than an arbitrary number of neutral red refractive bodies. This will be discussed later.

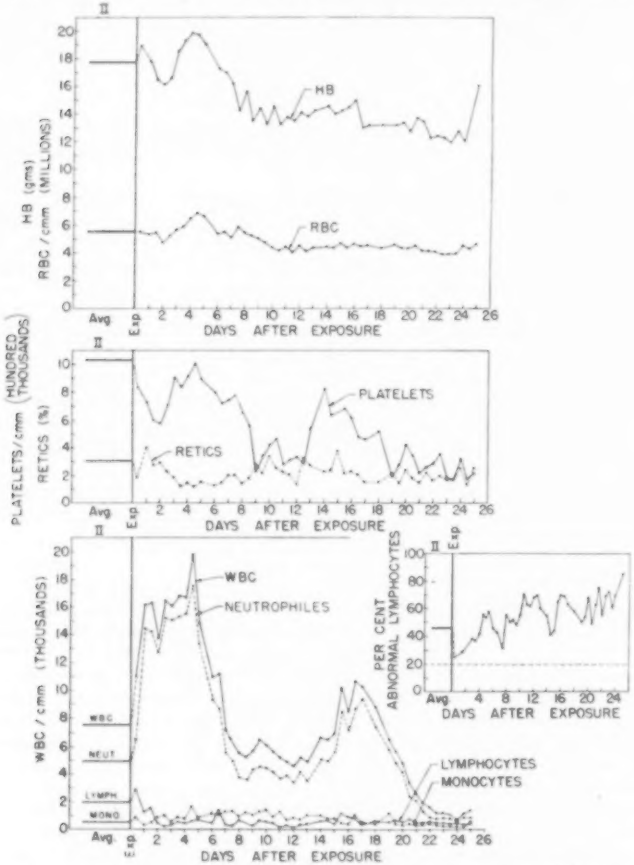
An interesting sequence of cytologic changes could be observed in the white blood cells after exposure, more evident in fixed films stained with Wright's stain than in supravital preparations. It is interesting to note in the following discussion that, of the three cell types, the lymphocytes appeared the most normal qualitatively until the terminal stages of the illness.

Lymphocytes (figures 2 to 6)

The lymphocytes showed progressive cytologic changes, more marked in the nuclei than in the cytoplasm. The first evidence of nuclear change could be observed in fixed films stained with Wright's stain during the latter part of the first week after exposure. This consisted of a gradual modification of the texture of the nucleus from coarsely basophilic to a smoother, less granular consistency that stained less intensely with hematoxylin. Simultaneously, there was a patchy condensation of chromatin with pale staining areas in between, which imparted a blotchy appearance to the nucleus. The nuclear changes progressed until many of the cells in the peripheral blood just before death appeared to be in the process of actual disintegration. There was complete loss of structure of the nuclei of many of the cells at this time with the formation of prominent intranuclear vacuoles (figures 2, 4 and 6). Some of the lymphocytes seen in the late stages of the illness showed hyperchromatosis of the nuclear membrane. Occasional lymphocytes showed shrunken pyknotic nuclei. The nuclei of some cells in the peripheral blood were very irregular in shape, with deep indentations which, in one of the observed cells, almost divided the nucleus in two (figure 5). One lymphocyte in the same film showed small nuclear pseudopodia. There was considerable variation in the depth of staining of the lymphocytes, with some cells staining so faintly that they presented a ghost-like appearance. One lymphocyte seen in the blood specimen obtained on the twenty-fourth day showed a disappearance of staining characteristics of about three-quarters of the nucleus; the rest of the nucleus and the cytoplasm appeared relatively normal (figure 3). Some

of the circulating lymphocytes in the peripheral blood on the day before death, however, were surprisingly normal in appearance except for minor nuclear changes.

The cytoplasm of the lymphocytes also showed changes. There was an increase in the cytoplasmic basophilia in young large cells as well as in the small lymphocytes.



Case. 1. The blood counts prior to exposure represent the average of 10 counts done over a period of one and one-half years at the Los Alamos Scientific Laboratory. (By permission of *Surgery, Gynecology and Obstetrics.*)

Vacuolation of the cytoplasm was noted by the end of the second week, at which time some lymphocytes were indistinguishable from the characteristic cells of infectious mononucleosis. Prominent basophilic cytoplasmic granules were seen on fixed smears (figure 6). No red azure granules were seen. There was an increase in the number of the neutral red-staining refractive cytoplasmic bodies which could be seen in supravital but not in fixed preparations.

In an effort to express quantitatively this increase in the number of the neutral red-staining refractive bodies seen in supravital preparation, it was decided arbitrarily to designate any lymphocyte containing more than five of these bodies as abnormal. The increase in the proportion of lymphocytes abnormal in this respect is shown in the accompanying chart (p. 304). It has been demonstrated previously that less than 20 per cent of the lymphocytes of persons not exposed to ionizing radiation or toxic chemicals show this abnormality (Dickie and Hempelmann, 1947).

The proportion of large young lymphocytes was increased in the terminal stages of the illness. These young cells showed the same nuclear changes as the small lymphocytes. There was an increase in the size of many of the lymphocytes.

Granulocytes (figures 7 to 9)

Toxic granules were seen in the polymorphonuclear neutrophils within 24 hours of exposure. There was a gradual decrease in the number of specific granules noted, particularly in supravital preparations, concomitant with the appearance of the large toxic granules (figures 7 and 8). These toxic granules became increasingly prominent and deeply basophilic until they all but obscured the nuclei of the cells in the terminal stage of the illness. They attained a size of 0.5 to 1.0 micron, and stained much more deeply with hematoxylin than did many cell nuclei. Although they varied in size from cell to cell, the granules in a single cell were quite uniform in appearance. There was some vacuolation of the cytoplasm of the neutrophil, but as a rule this was not so conspicuous as the toxic granulation. The cytoplasmic membrane of many of these large cells was faint and in some instances appeared to have ruptured, with discharge of the cytoplasmic granules. The toxic granules did not stain with metachromatic dyes, and their staining characteristics were not destroyed by incubation of the methyl alcohol-fixed films with ribonuclease.

The details of nuclear structure were difficult to see because of the toxic granulation of the cells. During the last week of the illness, many of the nuclei appeared to be swollen and pale. The nuclei of occasional cells showed prominent vacuolation (figure 9). The decrease in nuclear basophilia was very marked, particularly in the younger cells. A few nuclei of the neutrophils seen in the blood samples taken during the terminal phase of the illness were shrunken and pyknotic.

The neutrophils appeared to become much larger than usual; some of those in the blood the day before death had a diameter about three times that of the erythrocytes. The increase in size may have been due, in part, to the distortion of the cells during fixation.

During the initial granulocytosis, there was surprisingly little shift to the left in the hemogram. After the first week, however, an increasing number of "band" forms and metamyelocytes was seen. "C" myelocytes were occasionally found. The young cells showed marked toxic granulation.

Eosinophils were found even on the last day of the illness. They appeared relatively normal in appearance, although perhaps somewhat deficient in granules. Basophils could not be identified during the last week of the illness. It is possible that they were present but could not be distinguished from the toxic neutrophils.

Monocytes (figure 1)

The monocytes showed an unusual type of vacuolation of the nuclei beginning about the eighth day after exposure. This change was observed in all cells of the monocytic series. As it became more prominent, it imparted a "lacy" appearance to the nuclei (figure 1). During the last week of the illness, the nuclear vacuolation became so pronounced that many of the cells appeared to be on the verge of disintegration. The cytoplasm of the monocytes appeared relatively normal in some cells and was filled with small pink-staining granules in others.

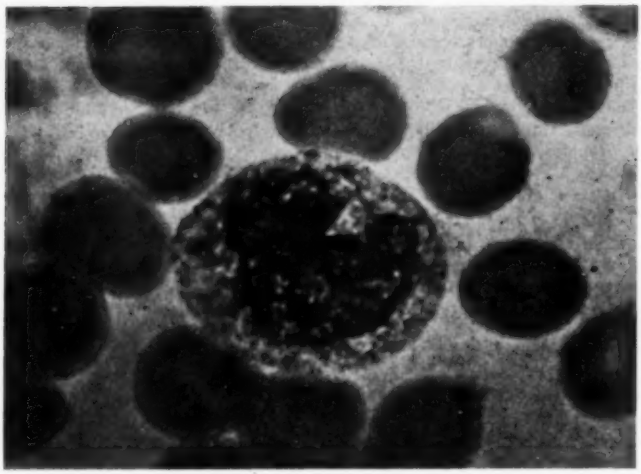


FIG. 1. Monocyte in blood smear taken on the tenth day after exposure. Note the "lacy" appearance of the nucleus due to vacuolation.

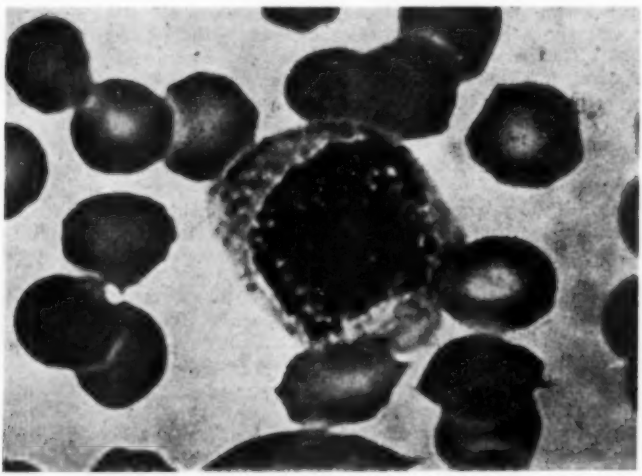


FIG. 2. Lymphocyte from blood smear taken on the twenty-fourth day showing the patchy deposition of chromatin in the nucleus. This cell is considerably larger than the usual lymphocyte.

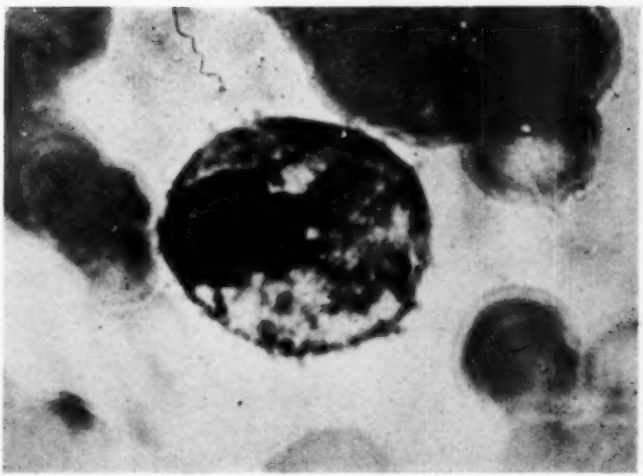


FIG. 3. Lymphocyte from blood smear taken on the twenty-fourth day after exposure. The cytoplasm and the portion of the nucleus in the upper left-hand corner appear fairly normal but most of the nucleus has almost completely disappeared.

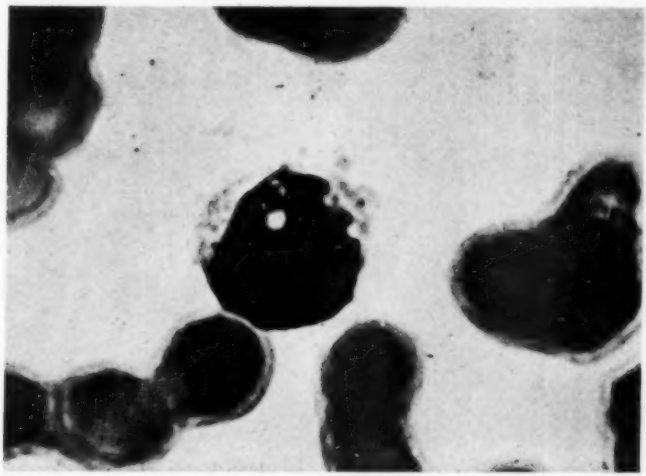


FIG. 4. Lymphocyte from a blood smear on the twenty-fourth day, showing marked vacuolation of the nucleus.

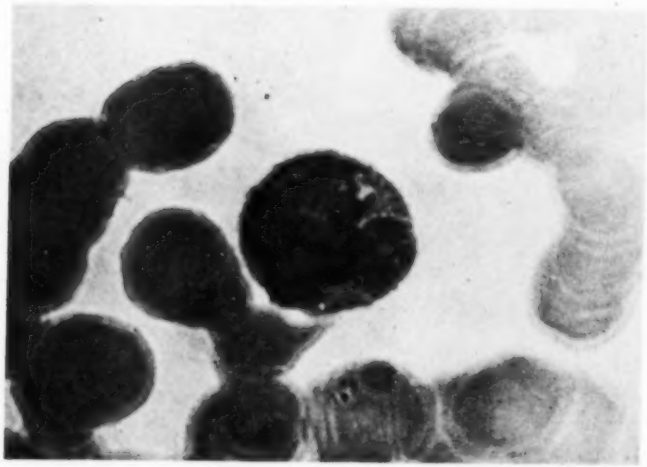


FIG. 5. Lymphocyte from a blood smear on the twenty-fourth day, showing marked irregularities of the nucleus. The right half of the nucleus appears shrunken.

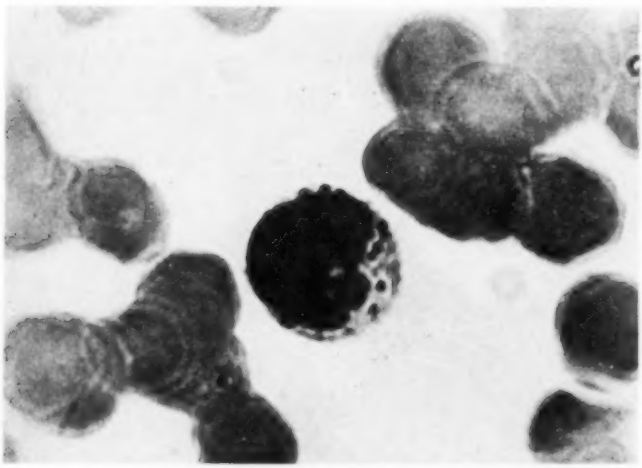


FIG. 6. Lymphocyte of the peripheral blood on the twenty-fourth day, showing some vacuolation of the nucleus and the large basophilic granules in the cytoplasm.

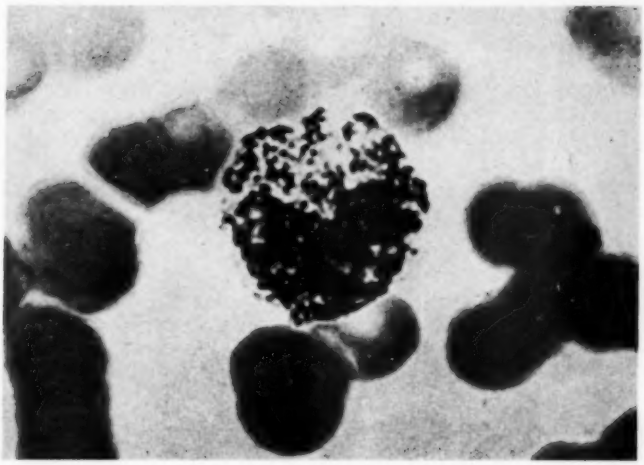


FIG. 7. Young neutrophil seen in the blood smear on the twenty-fourth day of the illness. Note the large deeply staining toxic granules and the very pale-staining nucleus.

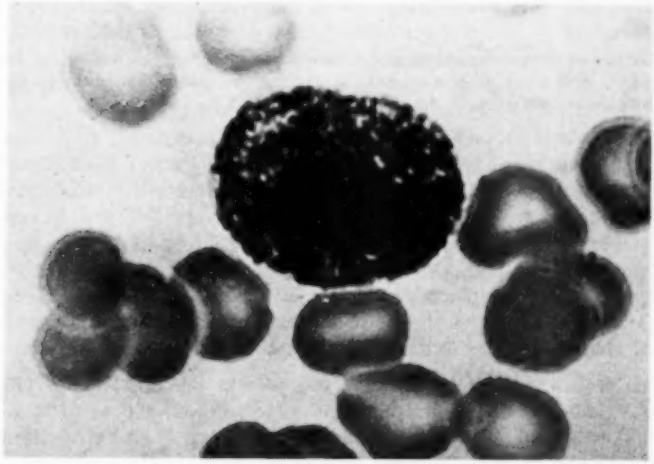


FIG. 8. Neutrophil in the blood smear taken on the twenty-fourth day, showing the very large, tightly packed toxic granules. The diameter of this cell is approximately 14μ.

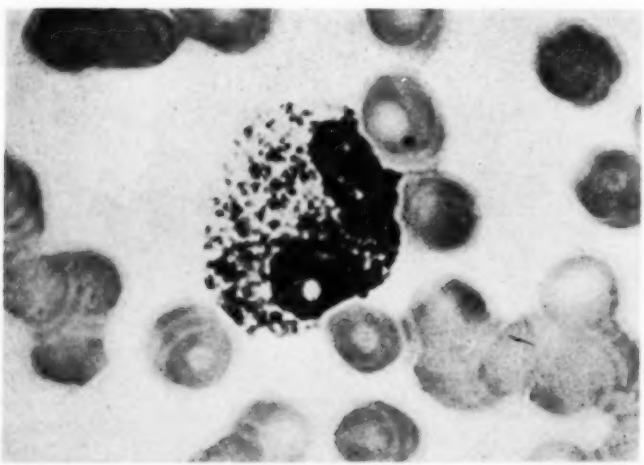


FIG. 9. Polymorphonuclear neutrophil from a blood smear on the twenty-fourth day, showing vacuolation of the nucleus and toxic granulation of the cytoplasm.

Erythrocytes

The red blood cells did not show significant morphologic changes.

Platelets

Platelets were evident, although in diminished numbers, even during the terminal stages of the illness. They seemed to be larger than normal in the supravital preparations during the last week of the illness.

Bone Marrow

Studies of the bone marrow were not done before death.

PATHOLOGY

See Appendix I-A for gross protocol and the following case summary for an abstract of the histologic observations.

SUMMARY

Clinical History

This patient, a 26 year old man, was seen at the Los Alamos Hospital within 30 minutes of the first accident. He received a dose of total-body radiation estimated to be equivalent to 480 roentgens of 80-kv roentgen-rays and 110 roentgens of gamma rays. His hands received considerably more radiation, equivalent to 5,000 to 40,000 roentgens of 80-kv roentgen-rays. He became nauseated within one and one-half hours and vomited intermittently for the 24 hour period following exposure. His blood pressure fell slightly. During the second day after the accident the patient's condi-

tion improved but he continued to be nauseated and to hiccough. From the third to the sixth day, the patient felt relatively well despite a slight fever. From the sixth day until death on the twenty-fourth day, the patient became increasingly toxic and lost a considerable amount of weight. The terminal rectal temperature exceeded 106° F. On the tenth day after exposure he developed a generalized stomatitis, mild paralytic ileus and diarrhea. The stomatitis reached its peak in several days and then subsided, only to reappear terminally in the form of necrotizing ulcers. The abdominal distention lasted only a few days. The diarrhea, however, persisted until death. Following intravenous medication on the fifteenth day, the patient had an attack of paroxysmal auricular tachycardia which lasted 24 hours. When the tachycardia ceased, electrocardiographic studies showed the heart to have nodal rhythm. Clinical signs of pericarditis were noted on the seventeenth day. Treatment of the systemic reaction consisted of the administration of penicillin, high fluid intake, thiamin chloride and two blood transfusions.

In addition to the severe toxic systemic reaction, the patient showed the progressive development of localized tissue destruction in both upper extremities and on the abdomen due to intense irradiation of these parts of the body. Both hands were swollen with a brawny edema within 30 minutes of exposure. The edema, more pronounced in the right hand and arm, spread to involve almost the entire upper extremities. This inflammatory reaction reached its maximum during the second week after the accident. The right hand began to blister 36 hours after exposure. The left hand, less heavily exposed than the right, did not show epidermolysis until the thirteenth postexposure day. The epidermolytic process spread until almost all the skin of the right forearm and that of the distal half of the left forearm had been lost by the time of death. Initially, the denuded surfaces exuded large quantities of yellow fluid, but during the second week the tissues became progressively less moist until, at death, there was dry gangrene of all the fingers of the right hand and of the thumb of the left hand. Some of the dermis showed superficial white ischemic necrosis. For the two weeks following the accident, the injured hands were very painful. Treatment of the injured tissues consisted of débridement and the use of pressure dressings. Drugs controlled the pain incompletely.

The skin of the patient's abdomen became erythematous on the third day and began to blister on the seventeenth day. All the epidermis of the abdomen and lower chest was lost by the time of death. This reaction was most severe and painful in the groin, where considerable maceration of the tissues occurred. The hair of the temples and beard started to epilate on the nineteenth day. Loss of hair was almost complete at the time of death.

Clinical Laboratory Findings

The leukocyte count showed an immediate granulocytosis which was sustained for five days, and a second relative increase in granulocytes from

the fifteenth to the eighteenth days. Lymphopenia developed promptly and was sustained. Agranulocytosis developed terminally. The erythrocyte count and the hemoglobin level showed a gradual decline after an initial increase during the fourth and fifth days. The platelets fell during the period from the eighth to the twelfth days and again terminally. The reticulocyte count did not change. There was a progressive increase in the proportion of lymphocytes containing an abnormally large number of refractive neutral-red staining bodies.

The lymphocytes showed a gradual change in the nuclear pattern, which progressed from patchy condensation of chromatin to frank disintegration, with conspicuous intranuclear vacuoles. The cytoplasm also became vacuolated, and prominent basophilic granules could be seen in films stained with Wright's stain. At the time of death, many of the circulating lymphocytes were dead or disintegrating, but some appeared relatively normal. The appearance of the neutrophilic granulocytes was modified sooner than was that of the lymphocytes. During the second day, the specific granules decreased in number and prominent toxic granules were seen. The toxic granulation increased progressively during the course of the illness. The nuclei of the neutrophils became pale and often showed vacuolation in the latter part of the illness. The proportion of young cells did not increase until the second week. The monocytes showed a peculiar type of intranuclear vacuolation. The platelets increased in size terminally.

The urine output was good throughout the illness. The specific gravity was always high. There was no albuminuria. A trace of bile and a positive urobilinogen test in a 1:100 dilution were observed in the last urine specimen. The stool became liquid but did not contain gross or occult blood except during the height of the gastrointestinal reaction. The quantity of corticoid-like substance * and amino acids in the urine was greatly increased on the twenty-fourth day. Radioactive sodium and phosphorus (induced by the interaction of neutrons and tissues) were measured in the urine excreted during the first day. Radiosodium but not radiophosphorus was also observed in the blood serum.

Pathology

Gross Findings: The body was moderately obese and showed evidence of recent weight loss. The most striking lesions noted on examination of the exterior of the body were (1) the extensive burns involving hands and forearms and the anterior portion of the midsection of the torso, and (2) the loss of hair in the bearded area and on the anterior part of the scalp. The burn on the body had a moist granular appearance, and the transition from denuded to normal-appearing skin was usually abrupt. There was pigmentation of a punctate nature around the margins of the burn. The burns on the swollen forearms had the same appearance as that on the abdomen, but the desquamated portions of the hands, particularly the right, had a

* The term "corticoid-like" is defined in Section VII-B-I.

white, opaque, parchment-like quality. There was advanced dry gangrene of all fingers of the right hand and of the thumb of the left hand. The loss of hair was almost complete in the bearded area, but was incomplete in the epilated portion of the scalp. The eyebrows showed some hair loss, and the remaining hairs could be pulled out easily.

Aside from the burns and the epilation, the only other findings of note in the external examination were the presence of several ulcers in the buccal mucosa and a slight yellow tinge to the skin.

Examination of the thoracic organs revealed an extensive serofibrinous exudate covering the pericardium of the hypertrophied heart, as well as a moderate amount of edema in the dependent portions of the lungs. The pericardial reaction was most striking over the left ventricle, where the thick exudate was hemorrhagic. Besides the hypertrophy of the myocardium of both ventricles, there were dilation of the right side of the heart and thickening of the endocardium over the interventricular septum.

The abdominal organs showed moderate enlargement and flabbiness of the liver and spleen. There was marked atrophy of the Malpighian bodies as visualized on the cut surface of the spleen. The intestine showed no abnormalities other than marked injection of segments of the ileum and a solitary ulcer in the transverse colon. The genitourinary organs were normal except for the presence of two ischemic infarcts in the right kidney and a decrease in size of the testes. The adrenal glands were normal in size and appearance.

The most obvious change in the appearance of the blood-forming tissues was the watery consistency of the red marrow. Although many lymph nodes were somewhat smaller than normal, those in the axillary and inguinal groups were swollen. The blood was clotted in an apparently normal fashion at the time of autopsy.

Microscopic Examination (See photomicrographs in Appendix I–A)

Skin: The basic lesions seen in the histologic sections of the skin consisted of (1) loss of the superficial layers; (2) necrosis of the surface of the denuded tissue, beneath which an inflammatory response consisting of infiltration of inflammatory cells (chiefly mononuclear), edema and dilation of vessels had occurred, and (3) regeneration of epidermis and dermis at the margin of the burns. The intensity and relative proportion of each reaction depended upon the region from which the sections were taken. Sections from the nongangrenous part of the right hand showed loss of part of the dermis as well as the epidermis. In contrast to the acellularity of the dermis of this region, there was a marked inflammatory reaction as well as proliferation of fibroblasts in the deeper subcutaneous tissues of the body. The skin of the torso showed loss only of the epidermis. The denuded dermis was covered by a layer of necrotic debris, fibrin and bacteria. In many regions, this surface exudate blended with the superficial layer of necrotic

dermis. Numerous plasma cells were found among the inflammatory cells; eosinophils were conspicuous but mast cells were rare.

At the edge of the abdominal burn a thin layer of regenerating epithelium was seen. The grossly intact epidermis in these sections was unusual in that there was a loss of normal cell differentiation and tissue architecture, as well as an abnormality in the appearance of many cells (variation in size and shape, particularly of the nucleus, inconsistency in chromatin content and vacuolation of the cytoplasm). Beneath this apparently newly formed epidermis there were marked proliferation of fibroblasts and sprouting of vessels, but little inflammatory reaction. Changes similar to those noted in the epidermal cells were seen in the hair follicles, particularly in their upper portions. While normal mitoses were seen in the epidermis, abnormal mitotic figures were seen in the cells at the neck of the hair follicles, and a complete absence of cell division was noted at the root. A striking change in epithelial cells had occurred in the ducts of the sweat glands, where varying and often marked degrees of squamous metaplasia were consistently observed. This change was most extreme in the heavily irradiated but still viable tissues of the hands.

Heart: The inflammatory reaction was limited to the pericardial surface, which was covered by a layer of fibrin containing red cells and mononuclear leukocytes, a few eosinophils and mast cells but no bacteria. The tissues beneath the surface showed an inflammatory reaction, with well developed granulation tissue in one section and hemorrhage in another. The heart muscle showed no significant abnormalities.

Lungs: Some fluid and hemorrhage in the alveoli as well as engorgement of the alveolar capillaries were noted.

Spleen: The Malpighian bodies were variable in size and showed no germinal centers. The white pulp was composed almost entirely of normal-appearing small lymphocytes and reticulum cells. The red pulp was intensely congested.

Gastrointestinal Tract: Beneath the ulcerated mucosa in the large bowel, there was infiltration of the submucosa with mononuclear cells of the lymphoid series and proliferation of fibroblasts. In the submucosa and fat underlying the fresh exudate and granulation tissue there was dense hyaline scar tissue. The mucosa at the edge of the ulcer showed complete loss of epithelium except for large abnormal cells in the deep-seated glands. The section of the ulcer in the buccal mucosa showed loss of epithelium, with a marked inflammatory reaction and considerable edema of the underlying tissues. Most of the superficial vessels were dilated and a few contained fresh thrombi.

Adrenals, Pancreas, Liver and Kidney: The histologic appearance of the adrenals and pancreas was not remarkable for the most part. However, some of the cells of the zona glomerulosa showed vacuolation which in some places had led to the dissociation of cells in the cords, with the formation of occasional small pseudotubules. No major lesions were observed in the

kidney except for the infarcts, which were relatively recent in nature and unusual only in that they showed mononuclear rather than polymorphonuclear cells at their periphery. The liver was essentially normal in appearance and showed only slight fatty infiltration.

Testes: The seminiferous tubules were small and shrunken and lined with Sertoli cells. No living spermatogenic cells were seen. The basement membrane of the tubules showed hyalinization. The interstitial tissue was edematous and apparently increased in amount. There were focal areas of degeneration of the muscle fibers in the ductus deferens, seminal vesicles and prostate. A moderately large number of mast cells was seen in some of these sections.

Lymphatic Tissues: Although some of the lymph nodes showed depletion of lymphocytes, the majority were quite cellular, with small lymphocytes forming the bulk of the lymphatic tissue. No cortical follicles with active germinal centers were found, but there was diffuse proliferation of lymphocytes. Although most of the small lymphocytes appeared normal, some intermitotic cells were disintegrating, and a few were dying in mitosis. In contrast, the medium-sized lymphocytes were mostly abnormal in appearance, with conspicuous, intensely basophilic cytoplasm and multiple nuclei. Many were undergoing the so-called "explosive" type of cell death during mitosis and showed bizarre chromosome aberrations. Although a few normal appearing large lymphocytes were found, a number of abnormal giant lymphocytes with deeply staining cytoplasm could be seen. The reticulum cells were prominent, particularly in the depleted nodes, but appeared normal, as did the endothelial cells. The blood vessels sometimes showed swelling and hyalinization of the intima and media associated with swelling and vacuolation of the endothelium. The sinuses of the nodes in the axillary and inguinal groups were distended with erythrocytes, debris and phagocytes.

Bone Marrow: The red marrow was decidedly hypoplastic, being perhaps one-third as cellular as normal. Immature cells of both the leukocyte and erythrocyte series were seen, with the former predominating slightly. About one in every three blood-forming cells was dead or disintegrating. The "explosive" type of cell death with bizarre nuclear aberrations was frequent. Reticulum and stem cells were numerous and well preserved. Hemorrhage and edema were noted in the fatty part of the marrow.

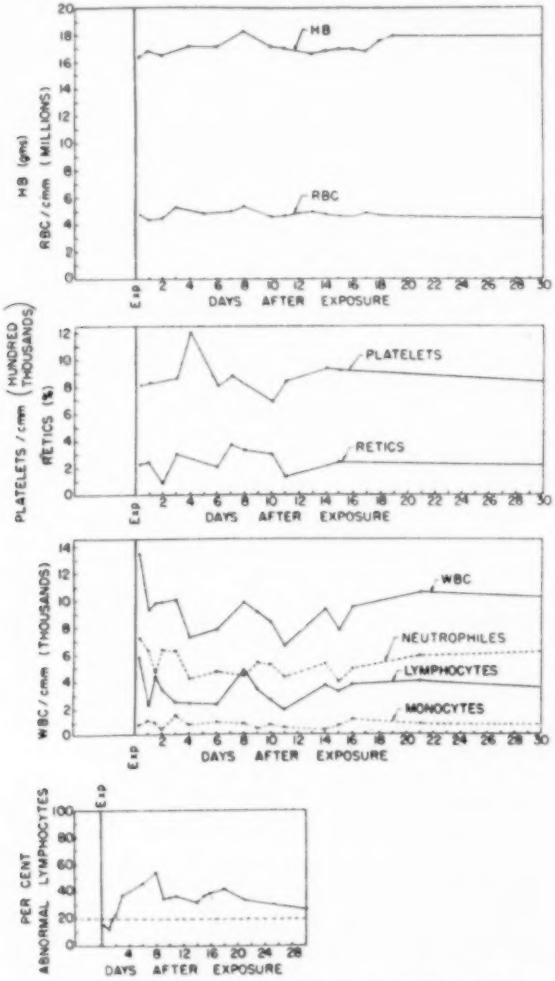
Anatomic Diagnoses: Severe second- and third-degree radiation burns (radio-dermatitis), involving skin of abdomen, lower part of thorax, upper portion of both thighs, both lower arms and hands. Advanced gangrene of all fingers of right hand; incipient gangrene of thumb of left hand; lymphadenitis of inguinal and axillary lymph nodes. Variable degrees of epilation of exposed areas of skin. Squamous metaplasia of excretory ducts of sweat glands. Hypoplasia of bone marrow and lymph nodes, with considerable and largely abortive regenerative activity. Atrophy of testes with complete aspermia. Ulcerative stomatitis. Serofibrinous pericarditis. Localized fibrosis of endocardium of left ventricle. Cardiac hypertrophy. Pul-

monary edema. Congestion of spleen. Ulcer of colon. Infarcts in right kidney.

Case 2

Clinical History

This 29 year old married man was admitted to the hospital within an hour of the first nuclear accident. He had been seated about 12 feet from the assembly, facing in



Case 2. No blood counts were done prior to the accident.

the opposite direction. The dose of radiation, delivered to his back, is estimated to have been equivalent to 31 roentgens of soft x-rays and 1 roentgen of gamma rays.

Past, social and family histories were irrelevant. The patient was married and the father of two children. He had not been exposed previously to ionizing radiation or toxic chemicals.

Medical Findings on Admission to Hospital

This patient presented no significant physical abnormality on admission to the hospital or on subsequent examination. The blood pressure on admission was 140/90 mm. Hg; temperature, 98° F.; pulse rate, 60 per minute; respiratory rate, 20 per minute.

He had no subjective complaint when first examined.

Course

The patient was kept in bed for two days after exposure. He experienced no gastrointestinal symptom. The blood pressure fell to 120/80 mm. Hg on the second day. Erythema, petechial hemorrhages, icterus and epilation were not noted. His weight did not change. He was released from the hospital on the third day but was not allowed to return to work for approximately two months. His only subjective complaint, subsequent to the accident, was moderate fatigability on exertion. This gradually disappeared in the course of about two months.

LABORATORY DATA—CASE 2

Neutron-Induced Radioactivity of Serum and Urine

Na^{24} Activity in Serum

Sample	Time Taken (hours after exposure)	c.c. Plated	mg. Na Plated	Na^{24} cpm. @ t = 20	Na^{24} Corr.* dps.	Na_{24} Corr.* dps./mg. Na
Serum I	17.4	5	16.8**	56	18	1.1

P^{32} Activity in Urine

Sample	Time Taken (hours after exposure)	c.c. Plated	mg. P Plated	P^{32} cpm. @ t = 0	P^{32} Corr.* @ t = 0	P_{32} Corr.* dps./mg. P
Urine I	17.4	25	5.3	70	25	4.7

N^{24} Activity in Urine

Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm. @ t = 0	Na^{24} Corr.* dps. @ t = 0	Na_{24} Corr.* dps./mg. Na
Urine I	17.4	3.00**	25	75	320	102	1.38

* Corrected for counter efficiency of 0.15.

**Inert sodium not determined chemically but assumed from tables of normal values.

Urinalysis and blood chemical studies were not done while this man was hospitalized. Subsequent examination of the urine revealed no abnormalities. The seminal fluid was not examined.

Examination 10 months after exposure revealed no significant change in the patient's physical condition. The blood pressure was 118/90 mm. Hg. He had no subjective complaint.

Follow-up

Examination of the patient four years after exposure showed him to be in good health. He had no complaint of any sort and has had two more children, born one and one-half and two and one-half years after the accident. He had gained about 15 pounds in weight. Except for moderate obesity and continued mild hypertension (138/90 mm. Hg), the patient's physical condition was within normal limits. The patient's endurance was tested, using the pulse rate after fatiguing exercises as an index of physical fitness, according to the procedure developed at the Harvard Fatigue Laboratory (Johnson, Brouha and Darling, 1944). His index was 84, a moderately good score considering the fact that the patient was overweight. Examination of his eyes, including study with a slit lamp, revealed no abnormality. Determination of the total and fractionated serum proteins and urea nitrogen showed them to be within normal limits. Liver function tests (cephalin flocculation, thymol turbidity and benzoic acid excretion) and renal function tests (phenolsulfonphthalein and concentration study) were normal.

Hematology

No blood count had been done before the accident. The changes in the blood count for the 30 day period after exposure are shown in the accompanying graphs (p. 316). The total leukocyte count remained constant at about 9,500 cells per mm.^{3} for five months after exposure. At this time it became quite unstable, presumably owing to a series of upper respiratory infections, and fluctuated between 7,000 and 15,000 cells per mm.^{3} On one occasion it fell to 4,600 cells per mm.^{3} The lymphocyte count consistently remained between 2,500 and 3,500 cells per mm.^{3} The absolute value for monocytes remained constant at about 1,000 cells per mm.^{3} The eosinophil count rose to about 450 cells per mm.^{3} from the seventh to the tenth months. The percentage of lymphocytes abnormal in content of refractive bodies remained between 20 and 40 during the entire 10-month period. There was no significant change in the erythrocyte count, hemoglobin level or reticulocyte count. The platelet count never fell below 400,000 cells per mm.^{3} during the five month period following exposure in which it was studied. No cytologic change in the formed elements of the blood was noted in the 10 month period following exposure during which the hematologic study was conducted at the Los Alamos Scientific Laboratory.

A sample of sternal bone marrow was aspirated 10 months after exposure. The marrow cells appeared normal, qualitatively and quantitatively. The megakaryocytes were adequate. The differential count follows.

	Per Cent
Leukocytes	
Granulocytes	
Neutrophils	
Segmented	11.00
Band	12.50
Metamyelocytes	30.50
Myelocytes "C"	16.50
Myelocytes "B"	8.50
Basophils	0.25
Eosinophils	2.25
Lymphocytes, small	13.75
Clasmatocytes	0.50
Clasmatocytes, phagocytic	0.75
Reticulum cells	2.00
Unclassified	1.00
Nucleated red blood cells per 200 leukocytes	158
Maturation of red blood cells	Normal

Examination of the blood four years after exposure revealed a total leukocyte count of 8,150 cells per mm.,[3] with 5,000 neutrophils, 1,790 lymphocytes, 815 monocytes and 490 eosinophils. The leukocytes showed no morphologic change. Only 2 per cent of the lymphocytes contained more than five refractive bodies. The red blood cell count was 5,070,000, with 17.7 gm. of hemoglobin. The platelet count was 877,040 per mm.,[3] and the reticulocyte count, 1.6 per cent.

Summary

This 29 year old man was hospitalized within an hour of exposure to a relatively small dose of total-body radiation estimated to be equivalent to 31 roentgens of soft x-rays and less than 1 roentgen of gamma rays. Physical examination on admission to the hospital revealed no essential abnormality. The patient experienced no subjective complaint except moderate fatigability for a two month period after exposure. He did not lose weight or show other signs of radiation injury. The only significant changes in blood count consisted of: (1) an initial transient leukocytosis; (2) a period of instability of the total leukocyte count five months after exposure, presumably due to a series of upper respiratory infections; (3) a mild eosinophilia seven months after exposure, and (4) a protracted increase in the number of refractive neutral red bodies in the lymphocytes. The patient's physical condition four years after exposure was unchanged except for a moderate gain in weight. He is the father of two children born after the accident.

Case 3

Clinical History

This patient, a 32 year old unmarried man, was admitted to the hospital within an hour of the second accident. He was touching the experimental assembly with his left hand when the nuclear reaction occurred. His arms and various portions of his body were exposed to widely different amounts of radiation. The parts of his body can be arranged in the following order according to decreasing dose: the hands and arms; the torso and upper thighs; the head; the lower part of the legs. It is impossible to estimate accurately how much radiation his hands received, but the dose of his left hand probably exceeded 15,000 rem (roentgen equivalent man) of soft x-rays, while that of his right hand was somewhat less. The radiation delivered to his body as a whole is estimated to have been equivalent to 1,930 roentgens of 80-kv x-rays and 114 roentgens of gamma rays.

The past family and social histories of this patient were not notable. His occupational history is interesting in that he had been exposed repeatedly over a three year period to small doses of whole-body ionizing radiation. The average weekly dose rarely exceeded 0.5 rem, but occasionally the exposure for a single day exceeded 0.1 rem. Repeated physical and laboratory tests had given no indication of radiation injury. Three years before, a few red blood cells and finely granular casts, but no albumin, had been noted in the course of routine urinalysis. There was no history of exposure to toxic chemicals.

Medical Findings on Admission to Hospital

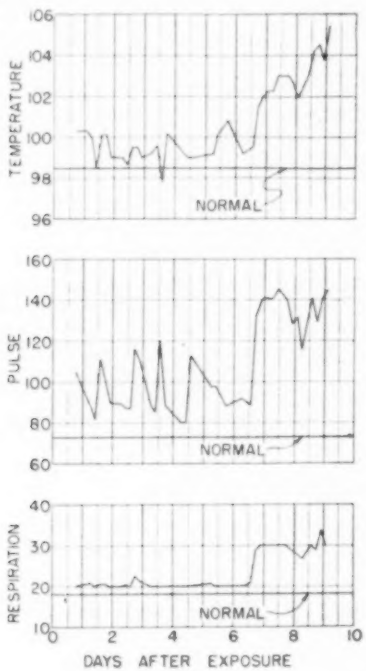
The patient was apprehensive on admission to the hospital and complained of nausea. He had vomited once prior to this examination, and vomited again several

times within the next few hours. He was well developed and appeared to be in excellent physical condition. His skin was bronze from the waist up as a result of repeated recent exposure to the sun. The heart, lungs and abdomen were normal. The hands showed no signs of injury. The oral temperature was 100.2° F.; the pulse rate, 104 per minute; respirations, 20 per minute, and blood pressure, 110/70 mm. Hg.

Course

Although the illness was not so complex as that described in case 1, the succession of events will be described by organ system.

General Condition: The general condition of the patient was good during the first five days of the illness. He was relatively comfortable, and his mental attitude and morale were excellent after he recovered from the early gastrointestinal reaction. On the fifth day, there was a precipitous fall in the leukocyte count. The following day the temperature and pulse rate rose abruptly. From this day on, the patient failed rapidly. There was obvious loss of weight during the terminal few days. On the seventh day, the patient had periods of mental confusion. He gradually sank into a coma and died quietly on the ninth day.



Case 3.

Extremities: Left Arm (Plates XIX to XXII): The left hand appeared normal at the time of admission to the hospital. Within three hours there was a slight erythema and swelling of the thumb, with cyanosis of the nailbed. The patient com-

plained of numbness and tingling of this finger. During the first 24 hours the hand became increasingly painful. The pain was described as burning in character and was associated with numbness. The swelling of the thumb increased rapidly, and 24 hours after exposure the entire hand and forearm were tensely distended with a firm nonpitting edema. The cyanosis of the thumb was more noticeable at this time. There was also a cyanotic tinge to the skin over the markedly distended interphalangeal joints. Sensation in the skin of the thumb and index finger was diminished. Twenty-eight hours after exposure a blister was observed on the thumb. It became larger rapidly and ruptured 40 hours after exposure, draining yellow fluid. The edema of the hand and arm increased until the swollen arm had a ligneous consistency and the skin a waxy appearance. There was no erythema. The burning pain became more difficult to control. On the third day, blisters appeared on the palm of the hand and on the interdigital surfaces of all fingers. The bullae on the palm and thumb became quite large (Plates XIX and XX). At this time the arm was packed in cracked ice continuously to control the pain and to stop the progress of the injury. Despite this therapy, the edema increased until the entire arm to the axilla was swollen. There was little extension of the blisters during the terminal six days of the illness and no sign of infection. The loss of blister fluid allowed the once tightly distended bulla on the thumb to collapse and the dead skin to become white and opaque (Plates XXI and XXII). The hands and arms remained intensely cyanotic throughout the chilling procedure. The cyanosis was blotchy at first but became uniform as it grew more intense.

Right Arm: The right hand, which appeared normal on admission to the hospital, became slightly swollen, stiff and somewhat painful during the first day after exposure. The swelling and pain increased during the second and third days (Plate XXIV), but this hand was, on the whole, not so severely injured as the left hand. The skin had a waxy appearance at this time; there was no significant erythema and no blistering. The extremity was packed in ice from the third day on. The tense nonpitting edema extended to the mid-forearm but there was no epidermolysis. The color of the chilled extremity became intensely cyanotic.

Skin: Twenty-four hours after admission to the hospital a slight erythema was noted on the lower, previously non-sunburned portion of the trunk and on the anterior surface of both thighs. The erythema increased in intensity, particularly in the region of the left lower quadrant and the left upper thigh. On the fifth day, the cutaneous reaction was associated with subcutaneous edema. The muscles underlying the erythematous area became sore and tender, and pain on motion limited the movement of the left leg. The erythema gradually increased in intensity and merged with the bronze color of the sunburned upper torso. During the eighth and ninth days the skin of the entire body became intensely flushed. There was no loss of skin, no blistering (except on the left hand) and no epilation.

Examination of the patient three hours before death revealed considerable extravasation of blood at the site of needle punctures. No evidence of spontaneous bleeding was apparent at the time of this examination but, at autopsy, small petechiae were noted on the skin of the right flank. Although the markedly injected conjunctivae and the suffused skin did not appear icteric during life, pronounced jaundice was evident after death when the blood had drained from the uppermost part of the body.

Gastrointestinal Tract: The patient vomited within an hour of exposure and again several times in the next few hours. One loose diarrheal stool was passed four hours after exposure. Vomiting and nausea ceased completely within 12 hours, and the appetite was good for the next five days. The initial gastrointestinal reaction of this patient was not nearly so severe as that in case 1. On the sixth day, the patient became nauseated, vomited and complained of abdominal distention which was unre-

lieved by enemata and rectal tubes. No peristaltic sound could be heard. The vomitus contained combined acid but no free acid and was guaiac-positive. The ileus became severe, involving not only the upper but also the lower abdomen. It caused the patient so much discomfort that gastric suction through a nasal tube was instituted and kept up almost continuously until death. Ten thousand cubic centimeters of green fluid with a fecal odor and appearance were aspirated during the first 24 hour period, with considerable relief of abdominal distress. Thereafter, smaller amounts of gastric fluid were removed, with good control of the distention. Symptoms recurred on the eighth day during a 12 hour trial period without the tube. Stools were solid and contained no occult blood until the seventh day, when the guaiac test became 4 plus. Thereafter, all stools were liquid, involuntary and guaiac-positive. No gross blood was observed in any stool specimen.

On the fifth day, the patient complained of soreness of his tongue opposite a gold inlay, and a small whitish ulcerated lesion was noted in this region. The inlay was capped with gold foil during the terminal four days. During the last two days of life the patient complained of dryness of his mouth and of thick postnasal mucus. On the day of death the mucous membranes showed no hemorrhage or ulceration.

Genitourinary Tract: Twenty-four hours after exposure the patient complained of pain in his testes, but there was no objective finding noted in the genitalia at this time or at any time throughout the illness.

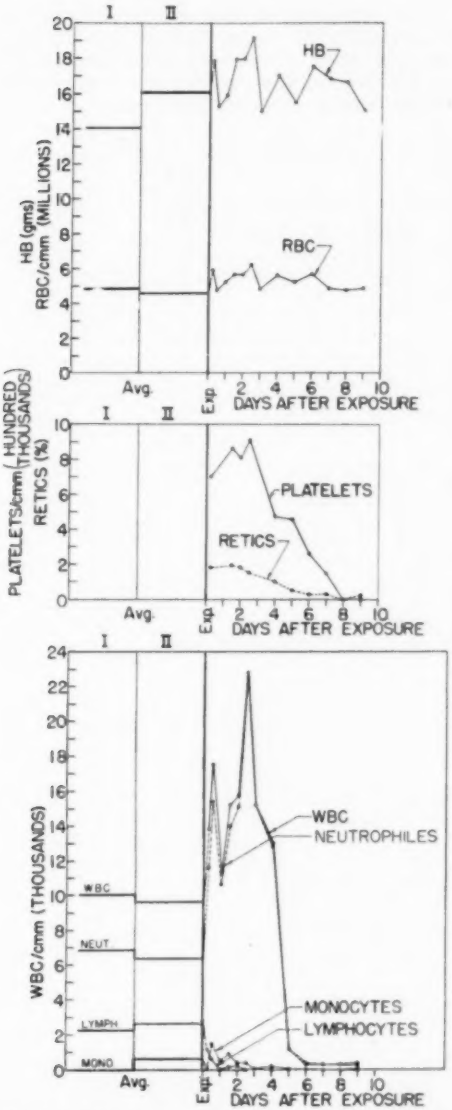
The urinary output during the first two days was diminished (500 to 600 c.c.) but thereafter was about 1,000 to 2,600 c.c. per day until the last day of life. No urine was voided during the terminal 30 hours. Examination of the urine showed increasing amounts of albumin, red and white blood cells and casts, beginning the second day after exposure. The non-protein nitrogen ranged from 57 mg. per cent to 161 mg. per cent on the last day of the illness.

Cardiorespiratory System: The initial blood pressure was 120/78 mm. Hg. It fell to 100/65 mm. Hg on the fourteenth hour and remained at this level for 10 hours. The systolic pressure returned to 120 mm. Hg 24 hours after exposure, but the diastolic pressure remained at the 65 mm. Hg level. After the second day, blood pressures were not taken because inflation of the cuff was painful to the patient. On the seventh day after exposure, the pulse and respiratory rate increased and the heart sounds became distant and tic-tic in quality, with a scratchy systolic component audible in the pulmonic area and suggestive of a pericardial rub. The heart was not enlarged to percussion. On the eighth day there was no essential change in cardiac findings except for an occasional skipped beat. On the ninth day the heart sounds were very faint but the rhythm was regular. The abnormal systolic sound was still audible over the pulmonic region and was heard, in addition, over the tricuspid area. The heart was not enlarged to percussion.

On the eighth day the patient's lips were cyanotic. He was placed in an oxygen tent, with prompt improvement in color. Respirations during the terminal hours were shallow, rapid and slightly irregular but not Cheyne-Stokes in character. The lungs were clear to percussion and auscultation throughout the illness.

Therapy

Therapy was purely symptomatic. The pain in the hands was controlled by ice packs and morphine for two days, and then by continuous refrigeration of the entire upper extremities. The pain in the lower abdomen was treated with ice bags. Therapy of the paralytic ileus consisted of continuous gastric suction after enemata and prostigmine failed to benefit the patient. Penicillin, 50,000 units intramuscularly every three hours, was given prophylactically after the fifth day because of agranulocytosis. Daily transfusions were given after the first day. Eleven pints of blood were



Case 3. The blood counts prior to exposure were done at the Metallurgical Laboratory, Chicago, and at the Los Alamos Scientific Laboratory. The average of 18 counts done in Chicago over a two-year period is shown in Period I. The average of five counts done at the Los Alamos Scientific Laboratory over a period of one year is shown in Period II.

given in eight days. Five hundred cubic centimeters of plasma and intravenous glucose in saline were also given during the first week. During the terminal three days, intravenous fluids were administered almost continuously. Eight thousand cubic centimeters of glucose in saline and 2,000 c.c. of lyophilized plasma, in addition to four pints of blood, were given during this period.

LABORATORY DATA—CASE 3

Urinalysis

Days After Exposure	Specific Gravity	Albumin	Microscopic
2	1.023	trace	2–3 RBC/HPF, mucus, hyaline and finely granular casts
4	1.019	+	6–8 WBC/HPF, few hyaline and finely granular casts
6	1.017	+++	5–8 WBC and 2–3 RBC/HPF, numerous hyaline and granular casts
8	1.012	++++	5–8 WBC, numerous RBC shadows, many granular casts

Stool Examination

Days After Exposure	Guaiac	Mucus	Description
3	negative	negative	formed
7	++++	negative	liquid

Gastric Analysis (Vomitus)

Days After Exposure	Free Acid	Total Acid	Guaiac
6	0°	50°	++++
8	0°	—	+++

Electrophoretic Blood Pattern

Days After Exposure	Nonprotein Nitrogen mg. %	Total Protein g. %	Albumin g. %	Globulin g. %			A/G
				α	β	γ	
9	163.0	7.03	2.78	2.64	0.75	0.85	0.65
Controls (Average 6 males)		6.45	3.57	0.96	0.98	1.06	1.24

Bacteriology

Days After Exposure	Specimen	Report
3	Blood	No growth in aerobic or anaerobic cultures
6	Blood	No growth in aerobic or anaerobic cultures
	Ulcer in mouth	*E. coli*, 90 per cent; gram-positive diplococci, 10 per cent
9	Blood (post mortem)	*E. coli* in both aerobic and anaerobic culture

LABORATORY DATA—CASE 3—*Continued*

Urine Chemistry

Days After Exposure	Corticoid-like Fractions			Coproporphyrin		Urobilinogen	
	a 220/240 mμ	b 240/260 mμ	a/b	μg. %	μg./day	mg. %	mg./day
1	1.28	1.36	0.94	1.8	—	trace	—
2 (12 hrs.)	1.47	1.17	1.25	2.4	—	0.02	0.1
5	0.93	1.62	0.57	18.8	186	0.06	0.6
6	1.09	1.40	0.78	25.5	451	0.16	2.8
7	1.70	1.18	1.44	25.1*	117	1.33	6.2
Normal range	1.5–1.7	0.9–1.1	1.4–1.8	4–9	30–100	trace to 0.2	1–4

Blood Chemistry

Days After Exposure	Serum Sodium mEq./l.	Chlorides mEq./l.	Urea Nitrogen mg. %	Non-protein Nitrogen mg. %	Uric Acid mg. %	Calcium mg. %	Icteric Index	Total Protein gm. %	Albumin gm. %	Globulin gm. %	A/G
1 (1 hr.)	140	—	—	—	—	—	—	—	—	—	—
2	134	75.3	10	—	3.4	—	—	—	—	—	—
3	132	—	—	—	—	—	—	—	—	—	—
4	133	67.8	—	57.0	—	—	—	5.4	4.1	1.3	3.1
8	—	68.3	24	—	5.6	8.8	—	7.9	5.8	2.1	2.8
9	—	63.0		161	—	9.4	70 (post mortem)	7.0	4.8	2.2	2.2

Urine Potassium*

Days After Exposure	Total Volume	mEq./24 Hours
1	310 c.c.	33.9
2	500	27.8
6	1770	163.7
8	466	38.4
Normal values**		40–65

* Analyses made with Beckman Flame Photometer.
** Hawk, Oser and Summerson, 1947.

Urine Amino Acids

Day of Illness	Cysteic Acid	Aspartic Acid	Glutamic Acid	Glycine	Taurine	Alanine	Valine	Leucine	Unknown Below Alanine	Unknown Below Valine	Other
1	0.1	0.1	0.1	1.0	0.75	0.5	0.25	0	0.25	0.1	Phenylalanine—0.1
2**	0	0.1	0.1	0.75	1.0	0.5	0.5	0	0.25	0	Phenylalanine—0.1
6	0	0.5	1.0	1.0	1.75	0.5	0.25	0.25	0.25	0	Serine—trace
7	0	0.5	1.0	1.0	1.0	0.25	0.5	0	0	0	Unknown—0.25 Arginine—0.1
Controls 3 cases 8–24 hrs.	0	0	0	0.1–0.25	trace	trace—0.1	trace	trace	0	0	Serine—trace Alanine—trace Arginine—trace 0.1

* Amounts expressed in mg./ml. (approximate concentration).
** 12 hr. sample.

LABORATORY DATA—CASE 3—*Continued*

Neutron Induced Radioactivity of Serum and Urine
Na^{24} and P^{32} Activity in Serum

Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm. @ t = 0	Na^{24} Corr.* dps.	Na^{24} Corr.* dps./mg. Na	p_{32} cpm./mg. P @ t = 0	p_{31} Corr.* dps./mg. P
Serum I	1.2	3.22	3	9.66	6,400	711	73.6	103**	12.8
II	46.9	3.09	5	15.45	10,240	1,137	73.6	bkg.	bkg.
III	66.1	3.03	5	15.15	10,700	1,177	77.8	—	—

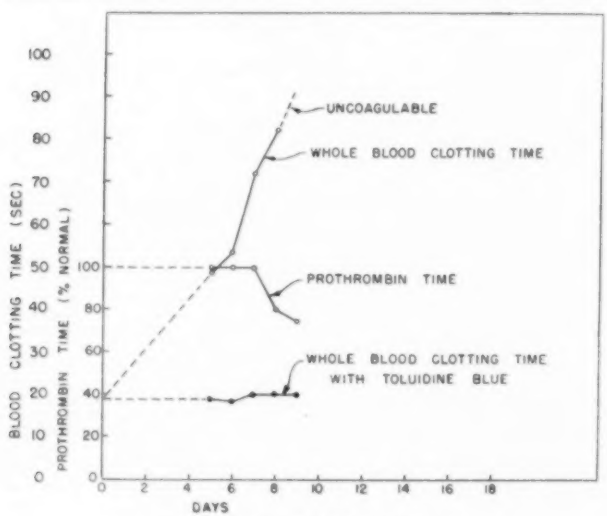
P^{32} Activity in Urine

Sample	Time Taken (hours after exposure)	mg. P/c.c.	c.c. Plated	mg. P Plated	P cpm. @ t = 0	P Corr.* dps. @ t = 0	P Corr.* dps./mg. P
Urine I	1.2	—	—	—	11,600	1,290	—
(Pooled) II***	3.8	—	—	—	3,200	356	—
(Pooled) III	5.3	0.256	5	1.28	4,120	457	357

* Corrected for counter efficiency of 0.15.
** Based on a 3 c.c. sample of serum which had 0.39 mg. phosphorus and 40 cpm. at t = 0.
*** Specimens passed at 1.2 and 3.8 hours were pooled.

Na^{24} Activity in Urine

Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm. @ t = 0	Na^{24} Corr.* dps. @ t = 0	Na^{24} Corr.* dps./mg. Na
Urine I	not run						
II	3.8	1.65	5	8.18	18,300	2,033	248



Case 3. **Blood clotting study.**

LABORATORY DATA—CASE 3—*Continued*

Radioactivity (P^{32}) in Tissues at Autopsy

Tissue	mg. P/gm. Tissue	mg. P Plated	cpm. @ t = 0	dps. Corr.* t = 0	dps./mg. = P Corr.*
Liver	2.55	12.7	29.0	2.9	0.228
Right kidney	1.46	4.25	2.9	0.29	0.068
Spleen	1.42	4.58	23.2	2.3	0.50
Right lung	1.62	4.32	4.8	0.48	0.111
Left lung	1.41	3.40	11.6	1.16	0.341
Rib	35.8	19.98	69.6	6.96	0.348

* Corrected for counter efficiency of 0.10.

HEMATOLOGY

Previous blood counts during the four years preceding the accident were not unusual. The total leukocyte count during this time was high, ranging between 7,500 and 12,000 cells per mm.,[3] except for a single count of 5,500 cells per mm.[3] one week before exposure.

The quantitative response of the formed elements of the blood is shown in the accompanying graphs. There was an immediate and marked granulocytosis lasting four days, and a prompt and persistent decrease in the lymphocyte count to a very low level. From the fifth day until death, all leukocyte types, platelets and reticulocytes were extremely rare. The red blood cell count and hemoglobin level rose during the first week.

The cytologic changes of the cells in the peripheral blood were similar to but differed somewhat from those described in case 1.

Lymphocytes (figures 10 to 12)

Cells of the lymphocytic series were extremely rare in the circulating blood, particularly during the last few days of life. Those observed on the eighth and ninth days varied in appearance from relatively normal-appearing lymphocytes (figure 10) to cells that had degenerated to the point where they could barely be identified. They varied in age from young cells with intensely basophilic cytoplasm to small mature lymphocytes. The degenerative changes took two forms, which were presumed to be different degrees of the same process. The first type of change consisted of an abnormal blotchy appearance of the nuclei with intervening areas of rarefaction. The second type of change consisted of vacuolation in varying degree of the nucleus and cytoplasm (figures 11 and 12). Some cells were so vacuolated that they appeared about to explode, whereas others showed minimal changes. One of the small lymphocytes showed a single large nuclear vacuole near the membrane which bulged into the cytoplasm, but otherwise this cell appeared normal. Many nuclei stained faintly with Wright's stain. There was no increase in cytoplasmic basophilic granules. The number of cells observed per blood sample was too few to give enough statistical information to permit the construction of a graph of lymphocytes abnormal in their refractive body content. The number of these bodies per cell was increased in the lymphocytes which were seen.

Granulocytes (figures 13 and 14)

Toxic granules were observed in the cytoplasm of the polymorphonuclear neutrophils in the samples of blood taken one hour after exposure. These granules increased in size, number and basophilia until just before death, when they were very prominent and stained more deeply with Wright's stain than many of the cell nuclei (figure 13).

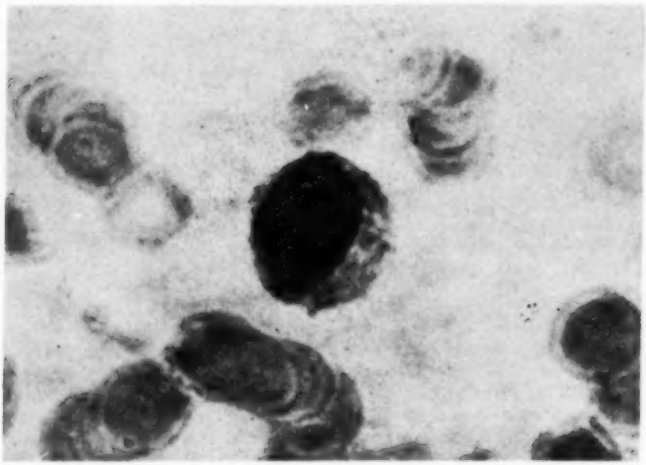


FIG. 10. Relatively normal appearing lymphocyte from the peripheral blood on the ninth day after exposure. It shows some patchy condensation of the nuclear chromatin.

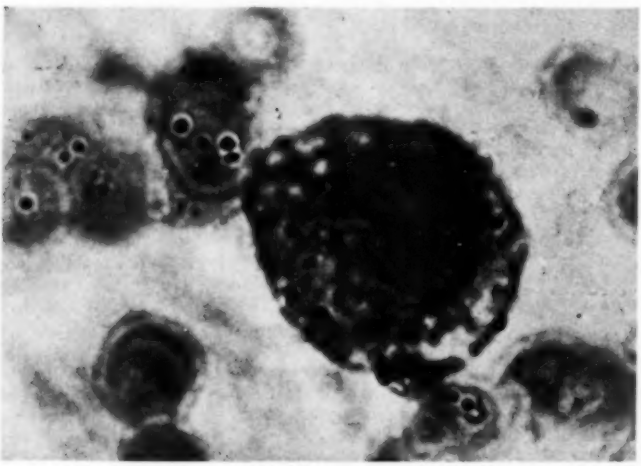


FIG. 11. Lymphocyte in blood smear taken on the ninth day showing the pallor of the nucleus and vacuolation of the cytoplasm.

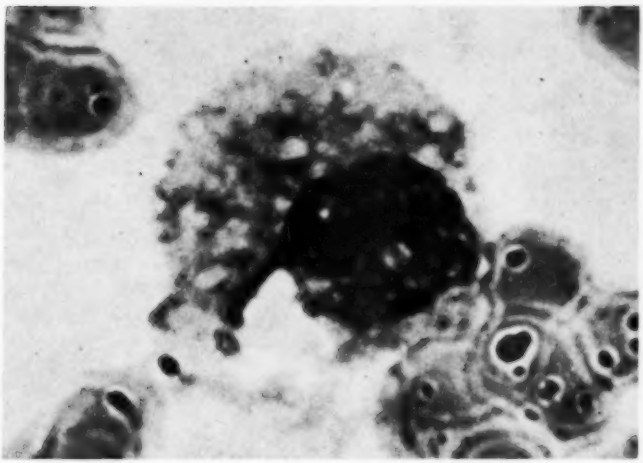


FIG. 12. Lymphocyte in the blood smear taken on the ninth day. The vacuolation of the nucleus and cytoplasm are prominent. Note the single very large nuclear vacuole in the lower left hand corner. The refractive areas seen in the erythrocytes are artefacts.

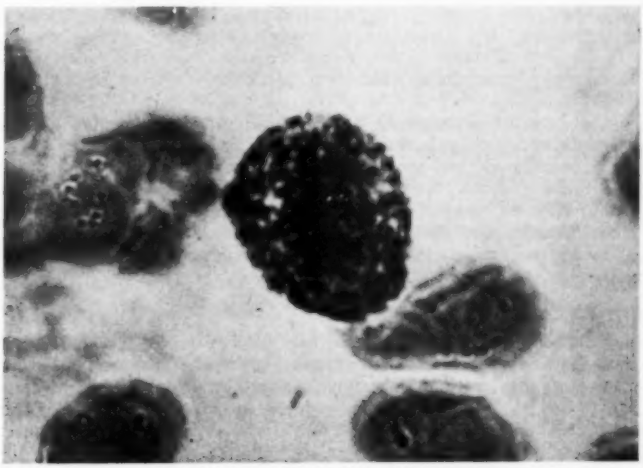


FIG. 13. Polymorphonuclear neutrophil in the blood smear taken on the ninth day of the illness showing toxic granulation and the pallid indistinct nucleus.

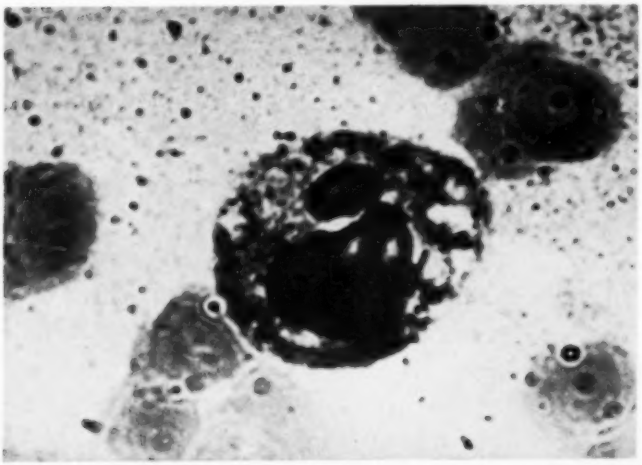


FIG. 14. Polymorphonuclear neutrophil in the blood smear taken on the ninth day showing vacuolation of the cytoplasm and nucleus. Note the unusually large nuclear lobe.

The toxic granulation noted on the ninth day was more notable than that observed in the neutrophils of case 1 the same number of days after exposure, but it was less marked than the granulation of case 1 the day before death (twenty-fourth day). This toxic change could be seen in neutrophils as young as "C" myelocytes, as well as in mature segmented cells. Occasional neutrophils showed very little change of this nature. In the terminal stages of the illness there was considerable vacuolation of the cytoplasm of many neutrophils, which was particularly evident in the supravital preparations.

The nuclei of many of the young cells seen in the fixed blood films taken on the eighth and ninth days were pale and swollen and occasionally vacuolated.

Most neutrophils did not show the marked increase in size noted in case 1. During the initial granulocytosis young cells of the neutrophilic series were not numerous, but after the granulopenia had developed the young cells outnumbered the mature ones. Classification of the young cells was difficult if not impossible in many cases because of the excessive toxic changes. No cell younger than "C" myelocytes was identified.

Monocytes

These cells became exceedingly rare by the fifth day, but those that were observed did not show the extensive intranuclear vacuolation described in case 1. By the third day after exposure, vacuolation of the cytoplasm was evident, and this progressed up to the time of death. There was an inconsistent increase in the granularity of the cytoplasm of the monocytes noted on various days. A few very young monocytes were observed on the day of exitus.

Red Blood Cells

Conspicuous rouleaux formation, observed in both fixed and supravital preparations, became increasingly prominent after the third day. The red blood cells varied somewhat in size during the late phase of the illness.

Platelets

The platelets appeared normal. They became increasingly rare during the last few days of the patient's life.

Bone Marrow

A specimen of bone marrow was obtained by sternal puncture on the second day of the illness. No gross clumps were obtained on three attempts to aspirate the marrow cavity. The marrow cells were so rare that it was impossible to do a differential count. A few "C" metamyelocytes were seen. Segmented neutrophils were seen around clumps of debris and degenerating cells.

Pathology

See Appendix I-B for gross autopsy protocol and Case Summary for an abstract of the histologic findings.

Summary

Clinical History

This 32 year old unmarried man was admitted to the hospital within one hour of the second accident. He is believed to have received a dose of total-body radiation equivalent to 1,930 roentgens of 80-kv x-rays and 114 roentgens of gamma rays. His hands received a larger dose, of approximately 3,000 to 30,000 roentgens. The only significant finding at this time was a slight elevation of the temperature (100.2° F.). The patient had vomited once before admission. During the first 12 hours after exposure, he vomited several times, passed one diarrheal stool and had a decreased urine output. He was moderately prostrated and showed a mild hypotension at this time. The initial reaction displayed by this patient was not nearly so severe as that in case 1. After the first day, his general condition was relatively good. On the sixth day after exposure the pulse and temperature rose abruptly, and the patient developed signs of severe paralytic ileus which could be relieved only by continuous gastric suction. The stools were diarrheal after the seventh day. At this time the heart sounds became distant, and on the following day the patient showed signs of circulatory collapse. Jaundice and spontaneous hemorrhages were not observed on the last examination several hours before death but were present at death.

Both hands of the patient suffered severe radiation damage. The left hand, the more heavily irradiated, showed edema, erythema and cyanosis of the nailbeds three hours after exposure. It became increasingly painful and began to blister 28 hours following the accident. The edema soon involved the entire forearm and was ligneous in character. From the third day on, the hand and forearm were packed in cracked ice. The epidermolytic process and pain were controlled by this procedure but the edema spread to involve the entire arm.

The right hand showed no erythema and less swelling than the left. It was also packed in ice continuously from the third day until death, even

though the skin did not blister. The edema extended only to the mid-forearm.

The patient also developed an erythema of the lower abdomen associated with edema and tenderness of the underlying tissues 24 hours after exposure. This erythema gradually spread and grew more intense until, at death, the skin of the entire body was deeply red.

Clinical Laboratory Findings

Leukocytosis (19,000 cells per mm.^{3}) and severe lymphopenia developed promptly after exposure. The monocyte count fell gradually during the first three days. The granulocyte count fell precipitously on the fifth day after exposure, but the platelet and reticulocyte counts showed a more gradual decline to very low levels. The erythrocyte count and hemoglobin level rose during the first week after exposure and then declined to the level before exposure.

The change in cellular pattern of the leukocytes was similar to that observed in case 1. The lymphocytes showed varying degrees of degeneration, ranging from an abnormal patchiness of the chromatin to frank intranuclear or cytoplasmic vacuolation. Just before death, however, some of the rare circulating lymphocytes in the blood showed only minimal degenerative changes. Toxic granules could be seen in the cytoplasm of the neutrophils one hour after exposure. This change became more pronounced as the illness progressed. Terminally, the nuclei were pale and swollen and the cytoplasm of individual cells was vacuolated. The monocytes showed cytoplasmic vacuolation but no consistent change in the nuclear pattern. The erythrocytes showed conspicuous rouleau formation but otherwise appeared normal. The appearance of the platelets did not change.

The clotting time of the whole blood became progressively longer until the blood was uncoagulated at the time of death. This abnormality in clotting could be nullified in vitro by the addition of toluidine blue to samples of whole blood.

The urine output was low throughout the illness, and the patient was anuric during the last 30 hours of life. The specific gravity of the urine samples showed a progressive decline, while the amount of albumin rose to 4 plus the day before death. Many pus cells and red blood cells were seen in the last specimen. The stools became liquid and guaiac-positive after the seventh day. The gastric fluid contained combined acid and occult blood on the sixth day after exposure.

Aerobic and anaerobic cultures of the blood were negative except for *Escherichia coli* in the heart blood at autopsy.

The blood chemistry showed an early fall in serum sodium and a late fall in blood chlorides. The non-protein-nitrogen and urea nitrogen of the blood were elevated on the fourth day and thereafter. The blood uric acid was slightly elevated. The icteric index at autopsy was high (70). The total serum proteins were not altered quantitatively to a significant degree.

but electrophoretic studies showed a moderate fall in albumin and a marked rise in alpha globulin.

Chemical studies of the urine showed an elevation of the corticoid-like substances in the urine and a marked increase in coproporphyrin and urobilinogen. They also indicated a striking amino-aciduria and a high urinary potassium on the sixth day after exposure.

Analysis of the induced radioactivity in the body fluids revealed surprisingly large quantities of radiosodium in the blood and of both radiosodium and radiophosphorus in the urine. The specific activity (ratio of radioactive to stable isotopes) of both the sodium and phosphorus was higher in the urine than in the blood serum. This difference was especially marked in the case of phosphorus.

Pathology

Gross Findings: The body showed good musculature with no evidence of wasting. The skin was dark yellow at the beginning of the autopsy but faded to ashen-gray. The sclerae were also jaundiced. There were petechial hemorrhages in the sclerae as well as in the skin. Massive ecchymosis was present in the right cubital fossa. Both hands were swollen, the left more than the right. The skin of the hands and forearms was pale gray. There were eight small blisters containing fluid and a large ruptured blister on the left hand.

The heart was normal in size and showed numerous fresh hemorrhages beneath the pericardium and endocardium, as well as a few smaller hemorrhages in the myocardium at the apex of the left ventricle. The lower lobes of the lungs were filled with blood-stained fluid and showed small patches of consolidation. The dependent bronchi contained aspirated gastric fluid.

Of the abdominal organs, the small intestine showed the most striking change. It was distended, flabby and filled with dark brown semi-liquid material. The vessels were intensely congested, and there were numerous petechial hemorrhages on the serosal surface. The mucosal surface was edematous and deep red, particularly in the region of the jejunum where, in addition, the surface was covered with a membranous gray-green exudate that could be stripped off in sheets. No discrete ulcer was seen. Petechial hemorrhages were found in the stomach and large bowel.

The liver and spleen were enlarged and soft in consistency. No Malpighian bodies were seen on the cut surface of the spleen. The adrenals were normal in appearance, as was the pancreas. The kidneys were enlarged and showed yellow streaking in the region of the pyramids. Petechial hemorrhages were found in the mucosa of the otherwise normal bladder. The testes were soft and small (21 to 23 gm.).

The red marrow was liquid in consistency. The lymph nodes, particularly those in the superficial groups, were smaller than normal. Those in the inguinal region could not be found.

On opening the body, streaks of yellow-gray were observed on the cut surface of the abdominal muscles. The blood did not clot during the autopsy except when in contact with the tissues for a prolonged period.

Microscopic Examination (See photomicrographs in Appendix I–B)

Skin: There was early vesicle formation in some sections of the abdominal skin. The epidermis showed evidence of marked damage. The usual sequence of cellular layers had been lost, and the cells, particularly in the basal layer, showed striking abnormalities (vacuolation of the cytoplasm, swelling of the nucleus, bizarre distribution of the chromatin, multiple nucleoli and absence of mitoses). The epithelial cells of the hair follicles showed changes similar to those in the epidermis, but the hair shafts appeared normal. The cells lining the ducts of the sweat glands had undergone squamous metaplasia. Despite the obvious proliferation of the duct cells, mitotic figures were not conspicuous.

Compared to the epidermis, the changes in the dermis were not striking. Nevertheless, edema and minute hemorrhages were noted, as well as infiltration by mast cells, degenerative changes in the nuclei of some connective tissue cells and dilation and endothelial swelling of vessels. There was also degeneration of the fat cells and muscle fibers in the deeper tissues.

Heart: The nuclei of individual muscle fibers showed more variation in size and shape than normal. Sections of the heart also showed hemorrhages, some infiltration by mast cells and edema of the interstitial tissues.

Lungs: The microscopic picture was that of terminal aspiration pneumonia in which polymorphonuclear leukocytic infiltration was absent; gram-positive bacteria, lymphocytes and phagocytes were prominent in the consolidated areas. In other areas there were pronounced hemorrhage and fluid within the alveolar spaces and intense congestion of the blood vessels.

Trachea: Large sections of the epithelium had desquamated, and in other regions the epithelium was present but had separated from the basement membrane. There was edema and round-cell infiltration of the connective tissues and patchy necrosis of the adventitial muscle fibers.

Spleen: The Malpighian bodies were decreased in size and, in some instances, had almost disappeared. No germinal center was seen. Many of the lymphocytes were abnormal and disintegrating cells were seen frequently. The most frequent mode of cell death appeared to be that which occurred during mitosis. The reticulum cells were normal in appearance. The red pulp was markedly congested.

Gastrointestinal Tract: The histologic changes in the mucosa were extreme throughout most of the gastrointestinal tract but were most pronounced in the jejunum and ileum. The sloughing epithelium of the esophagus was unusual in that there were numerous abnormal mitotic figures. The epithelial cells of the stomach did not show serious abnormalities. The epithelium of the duodenum had been lost except in the crypts, where most

of the cellular abnormalities already described were seen. There was complete erosion of the epithelium of the ileum and jejunum, as well as loss of the superficial layers of the submucosa. The epithelium of the colon was better preserved, particularly in the glands. Everywhere, the denuded surfaces of the intestines were covered by a layer of exudate in which masses of bacteria were seen.

Throughout the wall of the intestinal tract there was edema, congestion and a striking infiltration with round cells, mast cells and occasional eosinophils. Polymorphonuclear leukocytes were absent. In the ulcerated portions of the jejunum, bacteria had invaded the intestinal wall. The presence of granulation tissue in several parts of the submucosa of the jejunum indicated that a certain amount of repair had begun.

Liver: The sinusoids were congested. A few dead liver cells were found, and there was edema of Disse's space around the liver cords. No other important lesion was noted.

Adrenals: There was a widespread degenerative change in the cortical cells of the zona glomerulosa and fasciculata, more marked in the former. This consisted of vacuolation and even coagulation of the cytoplasm, occasional pyknosis of the nuclei, and accumulation of fluid between the cells and the basement membrane. There was little lipid in the zona fasciculata.

Kidneys: The glomeruli were congested but showed no significant change. The most important lesion was noted in the tubular epithelium and consisted of the presence of cytoplasmic vacuoles and hyaline droplets, many pyknotic nuclei and frankly degenerating cells. These changes were most obvious in the segments just below the glomeruli but were also apparent in cells lower in the proximal convoluted region. The cells of the remaining tubular epithelium were tall and their cytoplasm had a honeycombed appearance.

Testes: Severe damage was evident in the cellular components of the seminiferous tubules as well as in the interstitial tissues. The Sertoli cells were large and had pale, swollen nuclei that contained little chromatin material. No healthy germinal cells were seen. The lumina of the tubules were filled with necrotic cells and debris. The cells of the interstitial tissues were swollen and had large vesicular nuclei of peculiar configuration and bizarre chromatin arrangement. Mast-cell infiltration was prominent.

Lymphatic Tissue: There was severe depletion of all classes of lymphocytes, most pronounced in the mesenteric nodes, where only a framework of reticulum and connective tissue cells remained. At least two-thirds of the small lymphocytes were in some phase of cellular death, and those that seemed viable showed cellular changes consisting of generalized enlargement, increased ratio of cytoplasm to nucleus, pronounced cytoplasmic basophilia, and unusual distribution and staining characteristics of the nuclear chromatin. The medium-sized lymphocytes were more numerous than usual and frequently showed giant, multi-lobed or multiple nuclei. Many were in mitosis, but few were actually dying. Large lymphocytes were much in evidence and abnormal in appearance. Mitotic figures were numerous but

not so frequent as in the medium-sized cells. In sharp contrast to the dead and dying cells, discrete foci of regenerating lymphocytes could be found. The reticulum and endothelial cells and the debris-laden macrophages were generally well preserved and showed no mitotic activity. Numerous mast cells were interspersed among the lymphocytes.

The sinuses of the lymph nodes were engorged with precipitated lymph containing cellular debris, erythrocytes and fibrin. The walls of some of the blood vessels showed edema and swelling but no endothelial change.

Bone Marrow: The bone marrow was almost completely devoid of hematopoietic tissue, although a few stem cells could be found in the sections from the vertebrae. In these tissues precursors of the erythrocyte series outnumbered those of the white series. The rest of the sections of marrow were composed largely of distended sinuses and capillaries, with reticulum and fat cells constituting the only cellular elements. Except in the marrow of the femur, the reticulum cells, unlike those in the lymphoid tissue, were not well preserved.

Muscle: Degenerative changes could be seen particularly in the heavily irradiated striated muscle fibers of the abdomen, and also in the esophagus. The changes varied from foci of waxy degeneration to complete necrosis of the fibers, with some pyknosis and hyperchromatosis of the nuclei.

Nerves: No striking lesion was observed in the nerve fibers or Schwann cells, but the ganglion cells of the celiac, Meissner's and Auerbach's plexuses showed changes that probably were indicative of damage.

Adipose Tissue: The adipose tissue showed foci of degeneration accompanied by hemorrhage and edema. Many of the fat globules had broken down into smaller aggregates of lipid. In the periadrenal fat, the cells appeared collapsed and shrunken and partially bathed in edema fluid.

Anatomic Diagnoses: First and second degree radiation burns (radiodermatitis) of the skin of thorax, abdomen, upper portion of lower and lower portion of upper extremities and of both hands. Multiple blisters of skin of left hand. Squamous metaplasia of epithelium of excretory ducts of sweat glands. Aplasia and edema of bone marrow (panmyelophthisis). Severe depletion and hypoplasia of lymph nodes and of lymphatic system in spleen and gastrointestinal tract, with evidence of incipient and largely abortive regeneration. Necrosis and atrophy of seminiferous tubules of both testes. Diffuse membranous and ulcerative enterocolitis. Disseminated petechial hemorrhages. Jaundice. Focal necroses of cortical cells of both adrenals. Aspiration pneumonia, bilateral. Edema of liver. Focal tubular degeneration in proximal tubules of both kidneys. Fibromata in both kidneys. Waxy degeneration of abdominal and thoracic muscles.

Case 4

Clinical History

This patient, a 34 year old man, was brought to the hospital within an hour of the second accident. He was three feet away from the experimental assembly at the

time of the nuclear reaction. The radiation dose to his body was more uniformly distributed than was that in cases 1 and 3. He was turned slightly to the left when the reaction occurred so that the radiation entered the left anterior side of the body. He was partially shielded from the radiation, so that his head, shoulders and left arm received a greater dose than the rest of the torso. The average radiation dose to his body is calculated to have been equivalent to 390 roentgens of 80-kv x-rays and 26.4 roentgens of gamma rays.

The patient had been in good health before the accident. He was known to have a mild hypertension and to show intermittent albuminuria. He was married and had one child. The occupational history is pertinent in that the patient had worked with ionizing radiation for several years. His exposures were intermittent and were known to be well below 0.1 roentgen per day except on two occasions, when he received several roentgens in a week's period. He had not been exposed to radiation for 18 months before the accident.

Medical Findings on Admission to Hospital

The patient was in good physical condition. Examination revealed no physical abnormality other than a slightly elevated diastolic pressure (136/96 mm. Hg). The heart was not enlarged to percussion. No skin lesion was present. The oral temperature was 99.4° F.; the pulse rate, 100 per minute, and the respiratory rate, 20 per minute. The patient was calm and had no subjective complaints.

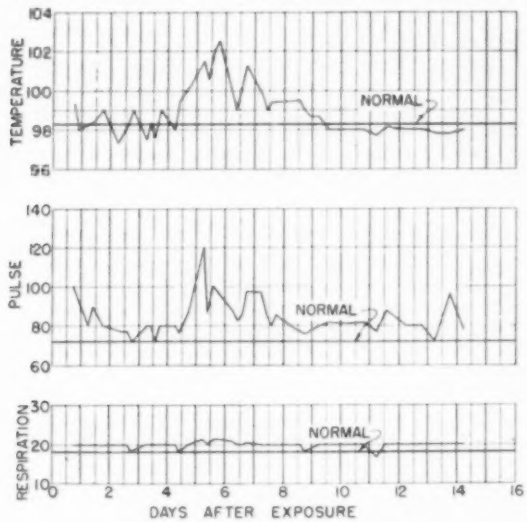
Course (figures 15 to 17)

The illness of this patient will be considered under three general headings: (1) general condition; (2) the reaction of the skin and its appendages, and (3) present status.

General Condition: Although he felt well on admission to the hospital, the patient vomited once several hours later. In the course of the next 12 hours the nausea disappeared and the patient's appetite returned. There was no diarrhea or other gastrointestinal disturbance. The blood pressure fell to 120/80 mm. Hg 14 hours after exposure and remained at this level for 24 hours, when it rose to the pre-exposure level of 140/90 mm. Hg. For several days after exposure the patient felt weak and tired and appeared prostrated but was otherwise asymptomatic. On the fifth day of the illness his temperature rose slightly. By the following day, the temperature had reached 102.6° F., and the patient complained of drowsiness, anorexia and constipation. His face was flushed, his abdomen soft and nontender. Penicillin therapy was instituted at this time on the chance that the signs and symptoms were due partly to infection. The temperature gradually fell to normal by the tenth day and the patient's condition improved. His appetite returned and he felt much stronger. His only complaint at this time, besides fatigability, was epistaxis on blowing his nose. Cauterization of Little's area of both nares resulted in prompt cessation of nasal bleeding. This procedure was also followed by the almost complete disappearance of the occult blood in the stools noted on the tenth day. There were no gastrointestinal symptoms at the time, and proctoscopic examination on the tenth day revealed completely normal mucosa in the rectum and lower sigmoid colon. The patient's strength improved steadily, and he suffered no untoward reaction to being allowed out of bed several hours a day after the tenth day.

Treatment of the illness was symptomatic: complete bed-rest for 10 days and penicillin, 50,000 units intramuscularly every three hours from the fifth through the eighth day. His fluid intake was kept above 2,500 c.c. per day. He was given 500 c.c. lyophilized plasma on the first and third days, two 500 c.c. blood transfusions on the third and fourth days, and several liters of intravenous fluids when fluid intake by mouth was diminished.

On the fifteenth day the patient was discharged from the hospital with instructions to rest at home for several weeks. Except for residual weakness and fatigability and some minor subjective complaints, he felt well. Physical examination at this time showed no change from the initial examination immediately after exposure



Case 4.

FIG. 15. Epilation of left side of head one month after exposure.
(By permission of *Surgery, Gynecology and Obstetrics.*)

except for a loss of weight (10 pounds). His blood pressure remained elevated slightly (135/90 mm. Hg). The mild increase in activity following discharge from the hospital was tolerated poorly by the patient. He tired easily after mild exertion and required 16 hours of bed-rest daily. During the first week after discharge from the hospital, the patient stated that he used more salt on his food than usual. There was a gradual return of strength and weight. By the end of the sixth week after

FIG. 16. Epilation of left temple two months after exposure. Note that the blond eyebrows are still present. The diminution in growth of beard on left side of face is evident.

exposure, the patient's weight had returned to normal and he was able to take a one mile walk without fatigue. Approximately 10 weeks after exposure, the patient's strength and endurance were back to normal and he returned to work. Since this time he has led an entirely normal life, working hard and engaging in outdoor sports.

Repeated seminal fluid and two testicular biopsy examinations during the 28 month period following the accident have indicated transient radiation sterility without change in libido or secondary sex characteristics. During the second year after exposure, the patient believed that the testes were smaller and were placed higher in the scrotum. Examination of the genitalia during this time indicated that the testes were within the limits of normal size, but the surgeon at the time of the first testicular biopsy (eight months after exposure) stated that the testes were softer than normal.

The patient believes that the testes have regained their normal position. Recent seminal examinations have indicated a rising sperm count.

Skin: The skin of the patient showed no erythema, icterus or petechia at any time during the illness. On the eighth day after exposure (three days after the start of penicillin therapy), an itching morbilliform rash appeared over the patient's body. Some of the lesions were urticarial in nature. Although the rash was present over the entire body, the lesions were most numerous over the elbows, knees and hands.

FIG. 17. Left profile four months after exposure showing complete regrowth of hair. The gain in weight since the first month is evident in this picture.

The rash disappeared in three days following the cessation of penicillin therapy, but residual itching of the skin persisted for about two weeks. The skin was clear on the day of discharge from the hospital, 15 days after exposure, but the patient complained of dryness of the skin of the forehead, the left hand and the groin. He also noted dryness of the mouth. There was numbness and some loss of tactile sensation of the skin of the left hand and forearm. Hypesthesia of the skin of both surfaces of the left hand and the dorsal surface of the left forearm persisted for about 10 days. The sensation of dryness of the skin and mouth gradually disappeared. Some desquamation of the skin of the hands and feet was observed one month after exposure. At this time the skin of the left hand appeared to be more flushed than that of the right.

LABORATORY DATA—CASE 4

Urinalysis

Days After Exposure	Specific Gravity	Albumin	Urobilinogen	Microscopic
2	1.024	0	—	Amorphous phosphates, no cells or casts seen
5	1.022	faint trace	positive 1:50	2–3 WBC and 3–5 RBC/HPF, mucus shreds, no casts
9	1.024	0	positive 1:10	2–3 WBC/HPF, mucus shreds, casts
14	1.010	faint trace	positive 1:10	Occ. WBC, amorphous urates, otherwise negative

(Occasional slight albuminuria noted previously).

Stool Examination

Days After Exposure	Mucus	Blood	Microscopic
2	0	0	negative
10	0	++++	negative
13	0	trace	negative

Blood Chemistry

Days After Exposure	Sodium mEq./l	Chlorides mEq./l	Urea Nitrogen mg. %	Uric Acid mg. %	Total Protein gm. %	Albumin gm. %	Globulin gm. %	A/G
1 (1 hr)	139	—	—	—	—	—	—	—
2	142	—	—	—	—	—	—	—
3	136	78.3	15	4.0	—	—	—	—
7	—	—	—	—	6.6	5.2	1.4	3.7
8	—	80.9	7	3.9	9.6	5.3	4.3	1.2
17	—	—	—	—	7.0	4.2	2.8	1.5
21	—	—	—	—	7.0	4.7	2.3	2.0
28	—	—	—	—	5.7	4.1	1.6	2.5

Urine Chemistry

Days After Exposure	Corticoid-Like Fraction Ratios			Coproporphyrin		Urobilinogen	
	a 220/240 mμ	b 240/260 mμ	a/b	μg. %	μg./day	mg. %	mg./day
1 (2 hrs.)				11.1			
(4 hrs.)				2.0	52	trace	trace
(13 hrs.)				4.5			
2	1.40	1.32	1.06	19.8	362	0.01	0.2
5	1.40	1.75	0.80	11.2	170	0.08	1.0
6	1.07	1.95	0.55	10.1	140	0.48	6.7
9	—	—	—	3.8	65	0.01	0.2
10	1.43	1.58	0.90	2.5	43	0.01	0.1
11	1.91	1.52	1.25	5.0	152	0.04	1.1
13	—	—	—	4.1	125	0.09	2.6
20	1.62	1.06	1.53	1.6	35	0.01	0.2
22	—	—	—	—	—	—	—
23	1.49	1.15	1.30	5.7	206	trace	trace
27	—	—	—	2.4	67	trace	trace
30	—	—	—	6.7	172	trace	trace
Normal range	1.5–1.7	0.9–1.1	1.4–1.8	4–9	30–100	trace to 0.2	1–4

LABORATORY DATA—CASE 4—*Continued*

Urine Potassium

Days After Exposure	Total Volume	mEq./24 Hours
4 hrs.	160 c.c.	9.3
1	660	16.8
2	1825	99.4
3	no volume recorded	43.5 mEq./liter
5	1520	76.0
8	1720	94.6
9	1710	90.7
10	3045	150.9
11	1795	125.1
12	3050	146.4
19	2200	79.2
21	no volume recorded	34.0 mEq./liter
22	3615	130.3
26	2780	111.1
29	2565	158.0
Normal value		40–65

Urine Amino Acids*

Day of Illness	Cysteic Acid	Aspartic Acid	Glutamic Acid	Glycine	Taurine	Alanine	Valine	Leucine	Unknown Below Alanine	Unknown Below Valine	Other
6 hr.	0.25	0.25	0.5	1.0	0.75	0.25	trace	0	0	0	arginine 0.1 unknown 0.1
1	trace	0.25	0	2.5	0.75	trace	0.1	0.1	trace	0	unknown 0.25
2	0	0.5	0.5	2.0	0.75	0.25	0.1	0.1	0.25	0	—
4	0.1	0.25	0.5	trace	1.0	0	0.1	0	0	0	—
6	0.25	0.5	0.75	1.5	1.0	0.25	0.1	0.1	0.1	0	arginine-trace
9	trace	0.25	0.25	0.5	0.5	0.25	0.1	0	0.1	0	—
10	0.25	trace	0.1	0	0.75	0	trace	trace	0	0	—
11	0.1	0.25	0.25	0.5	0.75	trace	0.1	0	trace	trace	—
12	trace	0	0.25	1.0	0	trace	0	0	0	0	—
20**	0.1	0.1	0.1	0	1.0	0	trace	0	0	0	—
22	0	0	trace	0.25	0	0	0	0	0	0	—
23	trace	0	trace	trace	0	0	0	0	0	0	—
27	trace	0	trace	0	0	0	0	0	0	0	—
30	0	0	trace	0	0.1	0	0.1	0	0	0	—
Controls 3 cases 8–24 hrs.	0	0	0	0.1–0.25	trace	trace-0.1	trace	trace	0	0	serine-trace alanine-trace arginine-trace-0.1

* Amounts expressed in mg./ml. (approximate concentration).
** Partial 24-hour sample.

Neutron-Induced Radioactivity of Serum and Urine
Na^{24} and P^{32} Activity in Serum

Sample	Time Taken (hours after exposure)	mg.Na/c.c.	c.c. Plated	mg.Na Plated	Na^{24} cpm.@ t = 0	Na^{24} Corr.* dps.	Na^{24} Corr.* dps./mg. Na	P^{32} cpm./mg. P @t = 0	P^{32} Corr.* dps./mg. P
Serum I	1.1	3.20	3	9.60	1,150	128	13.3	bkg.	bkg.
II	46.8	3.27	5	16.35	2,100	222	13.6	—	—
III	65.8	3.13	5	15.65	1,800	200	12.8	—	—

P^{32} Activity in Urine

Sample	Time Taken (hours after exposure)	mg.P/c.c.	c.c. Plated	mg.P Plated	P^{32} cpm.@ t = 0	P^{32} Corr.* dps. @t = 0	P^{32} Corr.* dps./mg.P
Urine I	1.2	1.22	5	6.10	2,630	290	47.5
II	3.1	0.101	5	0.505	310	34.4	68.1

* Corrected for counter efficiency of 0.15.

LABORATORY DATA—CASE 4—*Continued*

Na^{24} Activity in Urine

Sample	Time Taken (hours after exposure)	mg.Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm.@ t =0	Na^{24} Corr.* dps. @t =0	Na^{24} Corr.* dps./mg.Na
Urine I	1.2	2.94	5	14.7	2,000	222	15.1

* Corrected for counter efficiency of 0.15.

Studies on Erythrocytes

Days After Exposure	Sedimentation Rate	Mean Corpuscular Volume	Mean Corpuscular Hemoglobin	Mean Corpuscular Hemoglobin Concentration
17	0.75 mm./min.	81 cu. micra	27.4	34.2%
21	0.925	90	33.9	37.4
25	0.023	88	33.9	38.2
31	0.18	96.9	35.4	36.7

Normal values*	Min.	Avg.	Max.	Min.	Avg.	Max.	Min.	Avg.	Max.
	80	95.85	111	28	32.97	37.6	28	34.62	38

* One hundred normal males in Mexico City; elevation, 7,547 feet; (Gil and Teran, 1948).

The redness gradually turned to tan which persisted for several weeks. Three months after exposure, a rather prominent transverse ridging of the fingernails of the left hand was observed. The nails of the right hand showed no change.

On the seventeenth day after exposure the patient noted a localized area of tenderness of the skin of the left temple. The tenderness increased over a two-day period until touching the hairs of this region was painful. The patient noted no lesion of the scalp, but on the following day the hair of the left temple began to fall out on combing. Epilation increased until the hair could be pulled out by the handful with ease. Several days thereafter the patient noted diminished growth of his beard on his upper lip and chin and on the left side of his face and throat. These changes progressed to almost complete loss of the hair of the left temporal region and cessation of beard growth (figure 15). Regrowth of hair of the scalp and beard began slowly about one month after epilation was first noted. The growth rate of the hair of the head and beard was not normal for about four to five months. The new hair was indistinguishable from that on the rest of the scalp and beard in color and texture (figure 17). The eyebrows were not lost. There was temporary diminution in the amount of body and pubic hair.

Follow-up

The patient felt well 38 months after exposure. He was working extremely hard in a position of great responsibility and was taking moderately strenuous physical exercise, including skiing at high altitudes.

A physical examination 28 months after the accident indicated no physical abnormality. His weight was unchanged. The hypertension persisted. Laboratory studies, including exhaustive liver and kidney function tests, basal metabolism and blood chemistry studies, were within the limits of normal. The endurance of the patient was tested at this time, using the Index of Fitness for Hard Work developed at the Harvard Fatigue Laboratory (Johnson, Brouha and Darling, 1944). The patient's score was 93, which is considered good. The only evidence of injury at this time was a diminished sperm count.

Thirty-two months after the accident, examination of the patient's eyes showed an indistinct haziness in the posterior cortex of the lens of the left eye. Six months later, this lesion had developed into a moderately advanced radiation cataract in the posterior one-third of the lens cortex, with disc-like opacities and a subcapsular haze. There was also a questionable haze of the lens capsule at the posterior pole. Visual acuity of this eye was diminished (20/40), but the remainder of the examination of the eyes was normal. No change was observed in the lens of the right eye at this time. Physical examination (38 months after exposure) revealed no other findings. Laboratory findings at this time, including liver and kidney function tests and blood chemistry studies, were all within normal limits.

Fifty-eight months after the accident the patient became the father of a healthy normal male infant. He had developed an incipient cataract in the lens of his right eye and his visual acuity had changed slightly (O.D. 20/25, O.S. 20/200); otherwise the patient was in a state of excellent health.

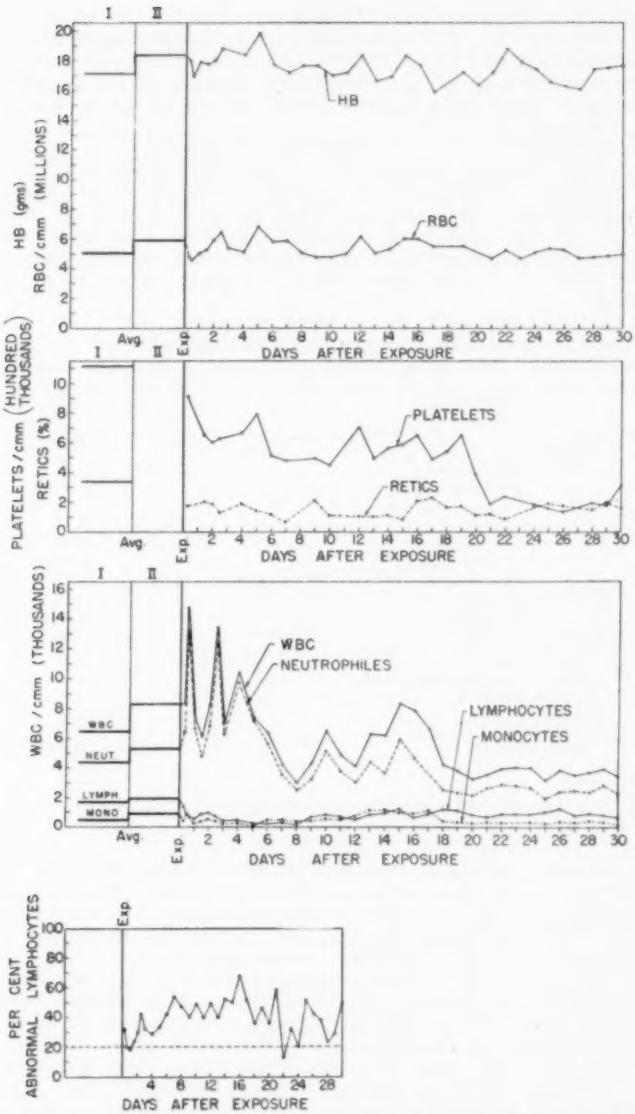
Hematology

All but one of the 16 preëxposure counts had been done several years before the accident. The total leukocyte count before the exposure ranged between 5,000 and 7,200 cells per mm.,[3] except for a single count of 10,800 when the patient had an abscessed tooth. The differential count had always been normal except for a mild transient lymphocytosis following whole-body exposure to several roentgens of gamma rays over a period of one week. The erythrocytes, hemoglobin, reticulocytes and platelets had been normal quantitatively.

The quantitative changes in the formed elements of the blood during the 30 day period following the accident are shown in the accompanying graphs (p. 345). The leukocyte counts during the first few days after exposure were high and showed considerable fluctuation. Following this, there was a leukopenia that was interrupted by an abortive rise in the granulocytes between the eighth and eighteenth days. The eosinophil count also decreased, but the monocyte count fluctuated and showed no sustained change. The lymphocyte count fell promptly and remained low throughout the 30 day period. The percentage of abnormal lymphocytes increased. The platelets fell on the eighteenth day to 100,000 to 200,000 per mm.[3] The count persisted for about 10 days at this level and then rose gradually to 400,000 by the fortieth day.

There were surprisingly few cytologic changes in the leukocytes except in the case of the polymorphonuclear neutrophils, which showed the prompt appearance of toxic granules and a deficiency of normal specific granules. This change was never so marked as that observed in cases 1 and 3, and it gradually reverted to normal beginning the latter part of the first month after exposure. Some cytoplasmic vacuolation of the neutrophils was observed in supravital preparations of blood during the third and fourth weeks. There was an increase in the number of young neutrophils beginning about one week after exposure and persisting until the end of the second month. Some of the lymphocytes showed equivocal changes in chromatin texture and pattern during the latter part of the second and third weeks. Young lymphocytes were numerous. There was a marked increase in the percentage of lymphocytes containing abnormal numbers of refractive bodies. There was no cytologic change detectable in the monocytes except for a rather pronounced granulation of the cytoplasm, more marked in some films than in others. Except for occasional basket cells, no frankly degenerating leukocytes were seen. The red blood cells showed an accentuation of the normal variation in size and shape. An unusually large number of microcytes was seen during the third week and thereafter.

Three bone marrow specimens obtained by sternal puncture were examined. The qualitative changes in the cells and the comments of the observer follow:



Case 4. Sixteen counts were done prior to the accident at the Los Alamos Scientific Laboratory. Fifteen of these were done over a period of 15 months that ended 18 months before the accident. The average of these counts is indicated in Period I. Period II represents a single count done 11 days before exposure. No counts were done between Periods I and II. (By permission of *Surgery, Gynecology and Obstetrics.*)

Second Day: "No clumps of bone marrow were aspirated. About 30 to 50 marrow cells were observed. They were mainly segmented neutrophils with a few scattered metamyelocytes and "C" myelocytes. There was considerable cellular debris and many fat globules, as well as numerous tissue basophils and two megakaryocytes. No nucleated red blood cells were seen. Marrow cells were too infrequent to justify a differential count."

Twenty-second Day (Dr. Carl V. Moore): "There were a few small clumps of marrow visible grossly in the aspirated specimen. Examination of these clumps showed that they were composed mainly of fat and cellular debris. Granulocytes were very infrequent. There was a moderate number of normoblasts. No megakaryocytes were seen. There was a moderate number of small round cells which were believed to be lymphocytes. While in general this specimen was consistent with the picture of profound aplasia, there were a few isolated islands of 50–75 normoblasts."

Seventy-eighth Day: "Only a few clumps of marrow could be seen grossly in the aspirated specimen. The cells appeared qualitatively normal but were not packed so tightly as usual. Only one megakaryocyte was seen. There was a lot of cellular debris and numerous phagocytic clasmatocytes." The differential count is shown below.

	Per Cent
Leukocytes	
Polymorphonuclear Neutrophils	
Segmented	11.25
Band	18.75
Metamyelocytes	27.00
Myelocytes "C"	23.75
Myelocytes "B"	1.25
Basophils	0.00
Eosinophils	2.00
Lymphocytes	10.50
Monocytes	0.00
Clasmatocytes, phagocytic	1.25
Reticulum cells	3.25
Plasma cells	1.00
Megakaryocytes	0.25
Primitive cells	0.00
	100.25
Nucleated red blood cells per 200 leukocytes	98
Maturation of red blood cells	Normal

Repeated blood counts in this Laboratory during the two-year period after the accident showed a gradual rise in the erythrocyte, granulocyte, lymphocyte and platelet counts. (See Appendix II.) The erythrocyte count reached its minimal value during the period from 40 to 70 days after exposure. It then rose slowly until one year later, at which time it had reached the 5,300,000 preëxposure level. The total leukocyte count rose gradually without great fluctuations to about 6,500 cells per mm.^{3} at the end of the second month. The maximal and minimal leukocyte counts have been 9,300 and 4,600 cells per mm.^{3} since recovery from the leukopenia which existed during the two-month period after exposure. The number of granulocytes remained about 3,000 cells per mm.^{3} until the seventh week after exposure, when it rose to over 4,000. It has fallen below this level only once since that time. There has been no significant change in the average number of lobes per granulocyte (Arneth's count). The lymphocyte count remained consistently low, about 1,000 cells per mm.,^{3} for over a year. During the second year there was an increase in lymphocyte count to a level of 2,000 cells per mm.^{3} There has been no essential change in the monocyte or

eosinophil counts after the second month. The platelet count has remained between 500,000 and 600,000 per mm.³ since the fiftieth day.

The percentage of "abnormal" lymphocytes remained elevated for about two years. About 40 per cent of the lymphocytes contained more than five refractive bodies during this period, except for a temporary fall to about 30 per cent for several months beginning four months after exposure. Twenty-eight months after exposure, there were 28.3 per cent abnormal lymphocytes.

A complete blood count 28 months after exposure showed 5.68 million red blood cells, 16.6 gm. hemoglobin, 3 per cent reticulocytes and 749,760 platelets per mm.³ The total leukocyte count was 7,100 per mm.,³ with 4,333 granulocytes, 1,988 lymphocytes, 568 monocytes and 71 eosinophils per mm.³ The last blood examination, 38 months after exposure, was essentially unchanged. The percentage of abnormal lymphocytes at this time was 10.

PATHOLOGY

Seminal Fluid and Testicular Biopsy Reports

Time After Exposure	Nature of Specimen	Count per mm.³	Comment
37 days	Seminal fluid	5,150,000	Nonmotile, 21% abnormal (10% large tails, 10% tailless, 1% double-headed).
80 days	Seminal fluid	1,450,000	Nonmotile, 8% abnormal (tail-less).
7 months	Seminal fluid	No sperm seen	—
10 months	Testicular biopsy	—	Many acini show complete atrophy with fibrous tissue replacement. Most tubules show fairly normal-appearing Sertoli cells with no spermatogenesis but occasional spermatids. The interstitial cells seem to be normal in amount and distribution. The tunica albuginea is thickened and fibrous and the walls of the blood vessels have an unusual amount of scar tissue.
15 months	Seminal fluid		Seven motile sperm seen in 20-minute examination.
20 months	Testicular biopsy		Marked atrophy of the seminiferous tubules, but beginning spermatogenesis is seen in several areas. No adult spermatozoa seen. The cells of Leydig are normal in number and appearance.
26 months	Seminal fluid	1,800,000	Motile sperm 70%, abnormal heads 15%.
50 months	Seminal fluid	10,800,000–16,000,000 (two samples)	1% abnormal sperm in both specimens; 40% motile in one sample, 60% in the other.
50 months	Testicular biopsy	—	(By Dr. John B. Storer.) There is considerable atrophy of both testes. In some tubules the germinal epithelium is completely denuded; in others, it is formed by a single layer of cells, chiefly Sertoli in type. A few areas show considerable regeneration of the germinal epithelium. In these areas mature spermatozoa are found. One can find all stages between complete destruction and complete regeneration of the germinal epithelium. There are a few areas of fibrosis in which there is obliteration of tubules. Impression: severe post-irradiation testicular atrophy with partial regeneration.

Summary

Clinical History

This patient, a 34 year old married man, was asymptomatic on admission to the hospital one hour after receiving a dose of total-body radiation estimated to be equivalent to 390 roentgens of 80-kv x-rays and 26.4 roentgens of gamma rays. He is thought to have been partially shielded from the radiations given off by the critical assembly in such a way that his head and left arm received a larger dose of radiation than the rest of his body. The patient was nauseated and vomited once within a 12 hour period following the accident. His blood pressure fell temporarily. After recovering from the initial reaction, the patient was weak and tired but otherwise well. On the fifth day after exposure he developed moderate fever, drowsiness, anorexia and constipation. Penicillin therapy was instituted for several days and the symptoms disappeared. An urticarial rash, presumably due to medication, developed on the eighth day. On discharge from the hospital 15 days after exposure, the patient felt well except for some residual weakness. He had lost some weight and noted dryness of the mouth and of the skin of his face and left arm. After leaving the hospital he was unable to tolerate even a moderate increase in activity and had to spend 16 hours a day in bed. Within 10 weeks of exposure his strength and weight had been regained. Seventeen days after exposure the left temple and beard began to epilate. Regrowth of hair was complete four to five months after exposure. The patient's physical condition was excellent three years after exposure. His endurance was not impaired. A moderately advanced radiation cataract but no other abnormal physical or laboratory finding was noted 38 months after exposure. He became the father of a healthy boy 58 months after exposure. A cataract has developed in the right eye.

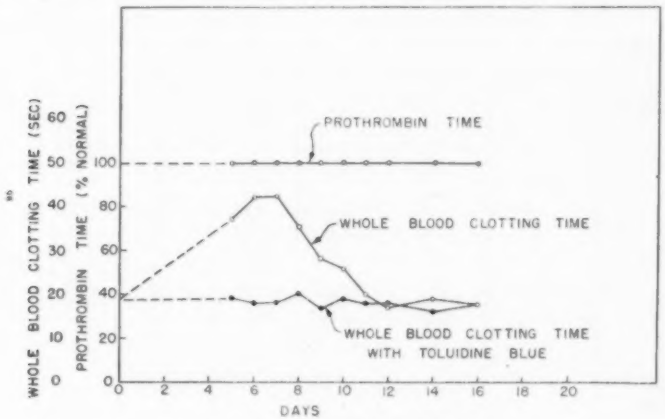
Clinical Laboratory Findings

The leukocyte count during the first day was high and for several days thereafter fluctuated between normal and high. Granulopenia developed on the fifth day. There was a temporary rise in the white cell count between the eighth and eighteenth days, and the granulocyte count gradually rose to normal by the end of the second month after the accident. In contrast, the lymphocyte count fell much more promptly and remained low for over a year. The eosinophil level was depressed from the fifteenth to the seventieth day and the monocyte count also fell slightly. The platelet count dropped to 100,000 cells per mm.^{3} and remained low for 10 days. The erythrocyte count (but not the hemoglobin level) decreased gradually and reached its lowest point between the fortieth and seventieth days after exposure. The lymphocytes showed a sustained increase in the number of neutral red refractive bodies but few cytologic changes in the nuclear pattern. Bone marrow studies showed extreme cell destruction on the second day after exposure, followed by a profound aplasia of all marrow elements.

Repeated urinalyses gave no indication of kidney damage. Stool examinations showed a 4 plus guaiac on the tenth day. There was no early change in the blood sodium or late change in the chloride or nitrogen content of the blood. The serum proteins were normal except for a questionable elevation on the tenth day. The amount of urinary corticoid-like substance was elevated. The urinary coproporphyrin was markedly increased, while the urinary urobilinogen was slightly increased on one occasion. The quantity of urinary amino acids was greater than that found in control urines, and the urine potassium level was also higher than that seen in healthy people on a normal diet. There were easily measurable amounts of radiosodium in the urine and blood. Radiophosphorus could be detected in the urine but not in the blood serum.

Pathology

Sperm counts and testicular biopsies disclosed a state of sterility from which the patient had recovered at the time of the last count, 50 months after exposure.



Case 4. Blood clotting study.

Case 6

Clinical History

This 54 year old unmarried man was admitted to the hospital one hour after exposure. He was standing six feet from the assembly at the time of the accident. It is estimated that he received the equivalent of 186 roentgens of soft x-rays and 10.7 roentgens of gamma rays, uniformly distributed over his body.

The past history was irrelevant. The patient was in the best of health and had always been active physically. He was in the habit of taking 20 to 40 mile hikes each weekend. There was no history of previous exposure to ionizing radiation or toxic chemicals. Repeated blood counts and urinalyses were normal.

Laboratory Data—Case 6

Urinalysis

Days After Exposure	Specific Gravity	Albumin	Urobilinogen	Microscopic
2	1.012	0	—	1–2 RBC/HPF
4	1.018	0	—	2–3 WBC/HPF, Occ. RBC, few spermatozoa
6	1.016	0	negative	—
8	1.007	0	positive 1:5	1–2 WBC/HPF, mucus shreds
10	1.023	0	positive 1:10	Few bacteria
15	1.015	0	positive 1:5	Occ. RBC, 1–2 WBC/HPF, mucus

Stool Examination

Days After Exposure	Gross	Guaiac	Mucus
4	Formed	—	0
10	Formed	—	0
15	Formed	trace	0

Urine Chemistry

Days After Exposure	Corticoid-like Fraction Ratios			Coproporphyrin		Urobilinogen	
	a 220/240 mμ	b 240/260 mμ	a/b	μg. %	μg./day	mg. %	mg./day
1 (4 hrs.)	—	—	—	2.5	—	trace	—
1	—	—	—	4.3	—	trace	—
2	—	—	—	5.7	25	trace	—
5	—	—	—	1.6	42	trace	—
6	0.92	2.63	0.35	4.2	128	trace	0.2
7	—	—	—	1.8	51	trace	—
8	—	—	—	5.5	97	0.04	0.7
9	—	—	—	4.1	97	0.01	0.3
10	—	—	—	1.9	63	0.02	0.7
11	—	—	—	1.7	62	0.03	1.2
12	—	—	—	2.6	67	0.01	0.36
19	1.43	1.59	0.90	2.9	85	trace	0.2
21	1.32	1.87	0.71	1.3	24	trace	—
26	—	—	—	—	—	0.03	0.9
29	—	—	—	—	—	0.02	0.3
Normal range	1.5–1.7	0.9–1.1	1.4–1.8	4–9	30–100	trace to 0.2	1–4

Blood Chemistry

Days After Exposure	Sodium mEq./l	Chlorides mEq./l	Urea Nitrogen mg. %	Uric Acids mg. %	Total Protein gm. %	Albumin gm. %	Globulin gm. %	A/G
1 hr.	141	—	—	—	—	—	—	—
2	138	—	—	—	—	—	—	—
3	—	71.9	10	3.8	—	—	—	—
8	—	80.9	14	4.4	8.0	4.5	3.5	1.3
14	—	—	—	—	6.5	3.9	2.6	1.5
19	—	—	—	—	6.9	4.5	2.4	1.8
23	—	—	—	—	7.8	4.8	3.0	1.6
27	—	—	—	—	6.8	4.8	2.0	2.4

LABORATORY DATA—CASE 6—*Continued*

Electrophoretic Blood Pattern

Days After Exposure	Non-Protein Nitrogen mg. %	Total Protein gm. %	Albumin gm. %	Globulin gm. %			A/G
				α	β	γ	
10	33.8	5.99	2.99	1.15	0.65	1.22	1.00
Controls (Average 6 Males)		6.45	3.57	0.96	0.98	1.06	1.27

Urine Amino Acids*

Day of Illness	Cysteic Acid	Aspartic Acid	Glutamic Acid	Glycine	Taurine	Alanine	Valine	Leucine	Unknown Below Alanine	Unknown Below Valine	Other
6 hr.	0	0	0	0	0	0	0	0	0	0	—
1	0	trace	0	0	trace	0	0	0	0	0	arginine—0.1
6	0	0	0	0	0.5	0	0.1	0	0	0	—
7	0	0	0	0	0	0	0	0	0	0	—
8	0	0	0	0	0	0	0	0	0	0	—
9	0	0	0	0	0	0	0	0	0	0	—
11	0	0	0	trace	trace	0	0	0	0	0	—
12	0	0	0	0	0	0	0	0	0	0	—
20	0	0	0	trace	0	0	0	0	0	0	—
23	0	0.1	0	0	trace	0	trace	0	0	0	—
24	0	0	0	0	0	0	0	0	0	0	—
30	0	0	0	trace	0	0	0	0	0	0	—
Controls 3 cases 8-24 hrs.	0	0	0	0.1–0.25	trace	trace—0.1	trace	trace	0	0	serine—trace alanine—trace arginine—trace—0.1

* Amounts expressed in mg./ml. (approximate concentration).

Neutron-Induced Radioactivity of Serum and Urine

Na^{24} and P^{32} Activity in Serum

Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm. @ t = 0	Na^{24} Corr.* dps.	Na^{24} Corr.* dps./mg. Na	P^{32} cpm./mg. P @ t = 0	P^{32} Corr.* dps./mg.
Serum I	1.9	3.25	3	9.75	620	69	7.1	bkg.	bkg.
II	46.7	3.16	5	15.80	540	60	3.8**	—	—

P^{32} Activity in Urine

Sample	Time Taken (hours after exposure)	mg. P/c.c.	c.c. Plated	mg. P Plated	P^{32} cpm. @ t = 0	P^{32} Corr.* dps. @ t = 0	P^{32} Corr.* dps./mg. P
Urine I	2.2	0.735	5	3.67	450	50	13.6

Na^{24} Activity in Urine

Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm. @ t = 0	Na^{24} Corr.* dps. @ t = 0	Na^{24} Corr.* dps./mg. Na
Urine I	2.2	6.01	5	30.5	2,100	233	7.75

* Corrected for counter efficiency of 0.15.
** Counting rate less than 100% of background.

LABORATORY DATA—CASE 6—*Continued*

Neutron-Induced Radioactivity of Body Tissues

Beta radiation from teeth, 30 hours after exposure, 850 cpm. on portable Geiger Unit

Studies on Erythrocytes

Days After Exposure	Sedimentation Rate	Mean Corpuscular Volume			Mean Corpuscular Hemoglobin			Mean Corpuscular Hemoglobin Concentration		
17	0.017 mm./min.	81.5 cu. micra			26.6			32.6%		
22	0.083	85			32.8			38.6		
25	0.008	83.5			32.6			39.0		
31	0.017	99.4			34.8			35.0		
		Min.	Avg.	Max.	Min.	Avg.	Max.	Min.	Avg.	Max.
Normal Values		80	95.85	111	28	32.95	37.6	28	34.62	38

* One hundred normal males in Mexico City; elevation, 7,457 feet; (Gil and Teran, 1948).

Medical Findings on Admission to Hospital

The physical findings on admission and during the period of hospitalization were entirely normal. The patient was in excellent physical condition. His blood pressure was 120/80 mm. Hg. He was partially bald. His skin was bronzed from exposure to the sun. There was a moderately severe gingivitis.

The patient's only symptom on admission to the hospital was a warm, flushed sensation in the skin of his face.

Course

The patient felt entirely well during the two week period of hospitalization. His blood pressure did not fall during the first day. He had no fever. His appetite was good. There was no nausea, vomiting or diarrhea. There was no other symptom referable to the intestinal tract, and proctoscopy on the tenth day revealed normal intestinal mucosa. No erythema, petechial hemorrhage or icterus was present. The patient's weight did not change. There was no epilation or loosening of the hair of the scalp. The patient did not complain of fatigability or weakness after leaving the hospital. Six weeks after exposure he walked 20 miles in one day over a mountain road at an altitude of 6,000 to 8,000 feet above sea level without undue fatigue or other ill effects. Thereafter, he resumed his usual practice of long, strenuous weekly walks. No study on spermatogenesis was carried out. Thirty-eight months after exposure, the patient was still well and able to work at his normal hard pace.

Follow-up

Examination 28 months after the accident revealed no change in the patient's physical condition. Slit-lamp examination of the lens of the eyes showed no evidence of scarring. All laboratory tests were within normal limits. These included kidney and liver function tests, basal metabolic rate, electrocardiography and blood studies. An endurance test 34 months after exposure, using the scheme developed by the Harvard Fatigue Laboratory, showed the Index of Fitness for Hard Work to be 103, a very good score for a patient of this age (Johnson, Brouha and Darling, 1942).

The last examination of the patient, 38 months after exposure, showed no change in his condition. Examination of his eyes revealed no abnormality. The laboratory data indicated normal liver and kidney function, normal blood morphology and normal blood chemistry. His Index of Fitness for Hard Work at this time was 99.

Hematology

The last blood examination before exposure had been done two years prior to the accident. The quantitative changes in the blood count during the first 30 days after exposure are shown in the accompanying graphs (p. 354). The most extreme change in blood count after exposure was an initial granulocytosis. Although the level of lymphocytes was low (about 1,000 cells per mm.^{3}), there was no return to pre-exposure level in a two year period after exposure. There was a mild, persistent eosinophilia, about 350 cells per mm.,^{3} starting about five days after exposure. The slight decrease in platelet count, to the 300,000 to 400,000 noted after the twenty-fourth day, was temporary; the count was back to normal (500,000 to 600,000) by the fortieth day.

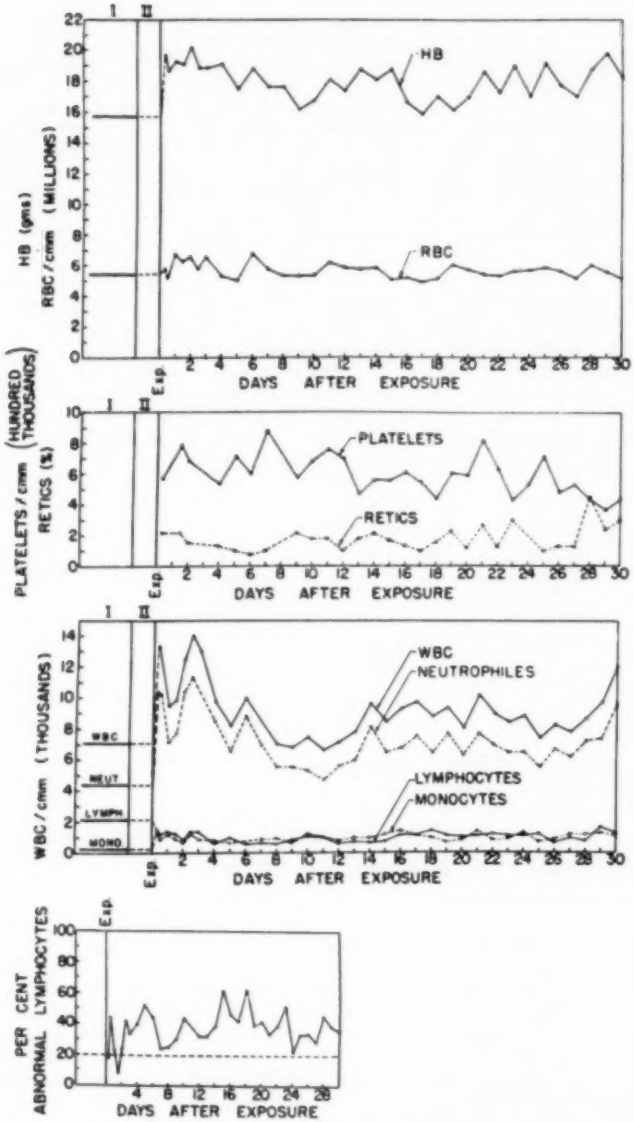
Minor cytologic changes were noted in the leukocytes of the peripheral blood during the first few weeks after exposure. Many of the neutrophils appeared mildly toxic in supravital preparation, but there was no significant shift to the left. There was no change in the number of lobes per neutrophil (Arneth's count) in the two year period after exposure. Some of the monocytes showed equivocal nuclear changes during the second week, suggestive of the "lacy" appearance described in case 1. The lymphocytes showed no significant cytologic change.

Sternal marrow aspirations on the twenty-second and seventy-eighth days after exposure showed the following marrow picture:

	22nd Day Per Cent	78th Day Per Cent
Granulocytes		
Neutrophils		
Segmented	7.5	11.00
Band	3.0	18.25
Metamyelocyte	15.0	21.75
Myelocyte "C"	45.0	19.75
Myelocyte "B"	2.5	2.00
Myelocyte "A"	1.5	—
Basophils	—	0.75
Eosinophils	0.5	2.75
Lymphocytes, small	18.0	14.75
Monocytes	1.0	—
Clasmatocytes, phagocytic	2.5	2.25
Reticulum cells	—	4.75
Primitive cells	—	—
Plasma cells	3.0	1.50
Megakaryocytes	—	0.25
Unclassified	0.5 Tissue basophil	—
Nucleated red blood cells per 200 leukocytes	455	81
Maturation of red blood cells	Normal	Normal

The following comments were made on the appearance of the two marrow preparations.

Twenty-second Day (Dr. Carl V. Moore): "Many rather large clumps of marrow were grossly visible in the aspirated specimen. Microscopically, there was a large amount of fat. The degree of cellularity varied considerably. Some of the clumps consisted almost entirely of fat and cellular debris, while others contained marrow cells. In the cellular portions there was a striking predominance of erythroid cells, mostly at the normoblastic stage of maturation. I think that the number of myeloid cells was definitely decreased but the cells seemed normal in appearance. Only a rather small number of the granulocytes showed vacuolation. Megakaryocytes were hard to find. There was a striking increase in the number of phagocytic clasmato-



Case 6. Six counts were done in Chicago one year before exposure. These are averaged in Period I. No counts were done at the Los Alamos Scientific Laboratory during Period II. (By permission of *Surgery, Gynecology and Obstetrics.*)

cytes and a moderate increase in tissue basophils. Some of the cells classified as lymphocytes may have been primitive cells of Sabin.

"I have the definite impression that this marrow is somewhat hypoplastic, particularly for myeloid cells and megakaryocytes. I have observed similar changes in the marrow of patients with blood dyscrasias who have received too much radioactive phosphorus."

Seventy-eighth Day: "Grossly, there were quite a few clumps of marrow. Microscopically, most of the cells in the clumps were normoblasts. No mature megakaryocytes were found. A few mitotic figures were seen in cells of the myeloid series. The number of lymphocytes was diminished."

In the two year period following the accident, blood counts at the Los Alamos Scientific Laboratory revealed a slight fall in erythrocyte count of questionable significance, most marked 40 to 70 days after exposure. The hemoglobin level barely decreased during this period. The absolute granulocyte count remained constant at about 6,500 cells per mm.,[3] except five months after exposure, when the number of granulocytes showed considerable fluctuation for a six month period, with a minimum of 3,900 and a maximum of 10,800 cells per mm.[3] There was no obvious clinical explanation for the instability. The absolute monocyte count has varied between 400 and 1,000 cells per mm.[3] The lymphocyte count has remained between 1,000 and 1,200. The eosinophilia increased two months after exposure and remained high for about one year. On two occasions the number of eosinophils per mm.[3] has exceeded 3,000. The eosinophilia was not present two years after exposure. The percentage of abnormal lymphocytes, i.e., those containing more than five refractive bodies, remained well over 20 for a year after the accident. During this time, the abnormal lymphocytes varied between 20 and 60 per cent of the total, with an average of about 40 per cent in the first few months. The percentage of abnormal lymphocytes gradually fell and, since the first year, has been below 20. The platelet count remained between 400,000 and 600,000 per mm.,[3] with no count below 300,000.

Complete blood examination, done several times between the twenty-eighth and the thirty-eighth months after exposure, showed the total leukocyte count to lie between 7,300 and 10,900 cells per mm.,[3] with 1,000 to 1,743 lymphocytes. The eosinophil count remained elevated, varying between 180 and 800 cells per mm.[3] The erythrocyte count was 5.5 to 6 million cells per mm.,[3] with 19 to 20 gm. of hemoglobin. The number of abnormal lymphocytes was 5 per cent on several occasions.

Summary

Clinical History

This 54 year old man received a large dose of ionizing radiation, yet he experienced no ill effect of any kind. His dose of total-body radiation is estimated to be equivalent to 186 roentgens of soft x-rays and 10.7 roentgens of gamma rays. He did not show epilation or lose weight. He was an active man and was able to take a 20 mile walk without undue fatigue six weeks after exposure. Three years after exposure, this man was well and fit.

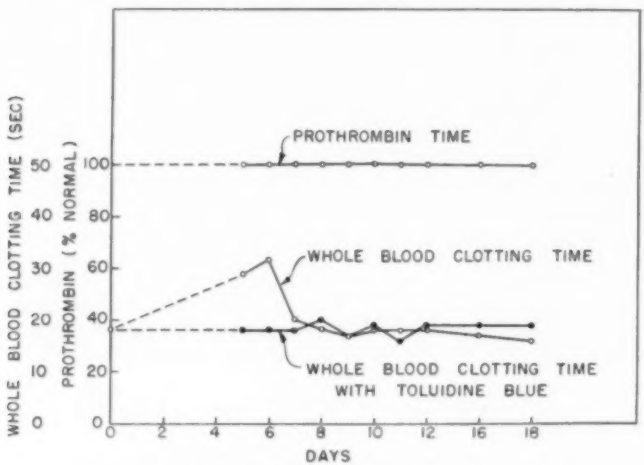
Clinical Laboratory Findings

The changes in blood count were: (1) an initial granulocytosis followed by instability of the total white count; (2) a prompt lymphopenia which persisted for two years; (3) an eosinophilia beginning five days after exposure, exceeding 3,000 cells per mm.[3] on two occasions and lasting for over a year; (4) a decrease in erythrocyte count of questionable significance,

reaching its maximum 40 to 70 days after exposure; (5) an increase in the number of refractive neutral red granules in the lymphocytes, and (6) a moderate aplasia of the sternal bone marrow. The clotting time was moderately prolonged at the end of the first week.

Urine examination revealed no abnormality. Stool examination showed an occasional trace of occult blood.

The blood sodium, chlorides, nitrogen and serum proteins were within normal limits. The electrophoretic pattern of the serum proteins showed a mild decrease in albumin and beta globulin. The amount of corticoid-like substance in the urine was increased for three weeks, but the quantity of excreted coproporphyrin and urobilinogen was not altered. Occasional urinary amino acids were found in increased amounts but there was no constant amino aciduria. Measurable amounts of radiosodium and radiophosphorus were found in the urine, while only the former was found in the blood.



Case 6. Blood clotting study.

Case 7

Clinical History

This 21 year old unmarried man was standing eight feet from the experimental assembly at the time of the accident. His body was uniformly irradiated by a dose of total-body radiation, estimated to have been equivalent to 140 roentgens of soft x-rays and 8.7 roentgens of gamma rays. He was seen one and one-half hours after exposure.

The past history is irrelevant except for an attack of rheumatic fever six years before which caused valvular damage to his heart. The patient had never been exposed previously to ionizing radiation or toxic chemicals. No blood count had been done before exposure.

Laboratory Data—Case 7

Urinalysis

Days After Exposure	Specific Gravity	Albumin	Bile	Microscopic
2	1.024	0	—	Mucus
4	1.031	trace	0	Numerous calcium oxalate crystals, 4–5 WBC/HPF, epithelial cells

Blood Chemistry

Days After Exposure	Sodium mEq./l	Chlorides mEq./l	Urea Nitrogen mg. %	Uric Acid mg. %
1 (1 hr.)	140	—	—	—
2	—	70.1	9	3.6

Blood-Clotting Studies

Clotting and prothrombin time were within normal limits

Urine Chemistry

Hours After Exposure	Corticoid-Like Fraction Ratios			Coproporphyrin		Urobilinogen	
	a 220/240 mμ	b 240/260 mμ	a/b	μg. %	μg./day	mg. %	mg./day
(1–12)	1.72	0.98	1.76	—	—	—	—
(12–24)	—	—	—	10.1	126	0.02	0.3
Normal Range	1.5–1.7	0.9–1.1	1.4–1.8	4–9	30–100	trace to 0.2	1–4

Urine Amino Acids*

Day of Illness	Cysteic Acid	Aspartic Acid	Glutamic Acid	Glycine	Taurine	Alanine	Valine	Leucine	Unknown Below Alanine	Unknown Below Valine	Other
6 hr.	0	0	0	0	0.1	0	0	0	0	0	—
1½	trace	trace	trace	0	0.5	0	0	0	0	0	—
Controls 3 cases 8–24 hrs.	0	0	0	0.1–0.25	trace	trace—0.1	trace	trace	0	0	serine—trace alanine—trace arginine—trace—0.1

* Amounts expressed in mg./ml. (approximate concentration).

Neutron Induced Radioactivity of Serum and Urine

Na^{24} Activity in Serum

Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm. @ t = 0	Na^{24} Corr.* dps.	Na^{24} Corr.* dps./mg. Na
Serum I	1.8	3.22	3	9.66	260	29	3.0

P^{32} Activity in Urine

Sample	Time Taken (hours after exposure)	mg. P/c.c.	c.c. Plated	mg. P Plated	P^{32} cpm. @ t = 0	P^{32} Corr.* dps. @ t = 0	P^{32} Corr.* dps./mg. P
Urine I	1.2	1.27	5	6.35	170	18.9	2.97

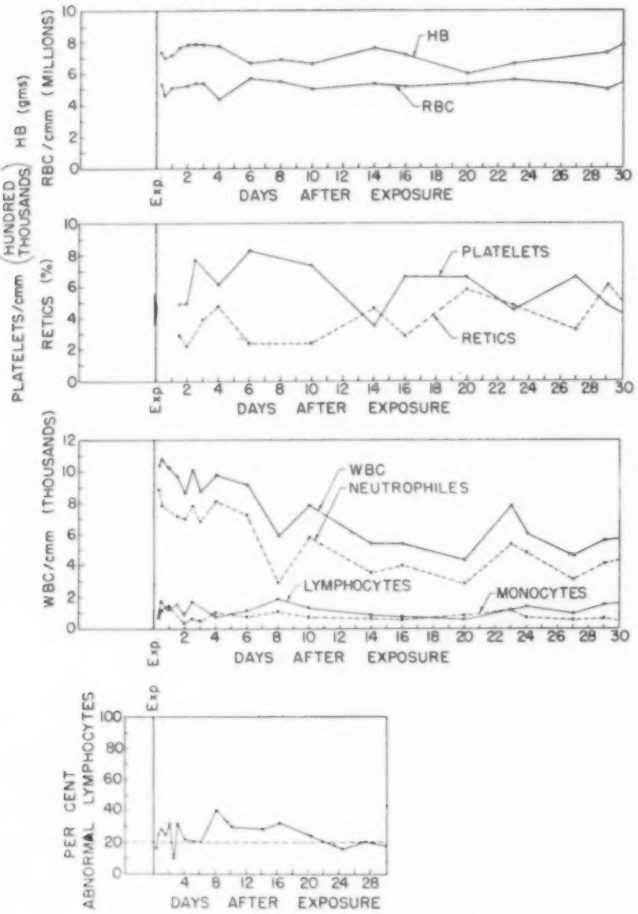
* Corrected for counter efficiency of 0.15.

LABORATORY DATA—CASE 7—*Continued*

Na^{24} Activity in Urine

Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm. @ t = 0	Na^{24} Corr.* dps. @ t = 0	Na^{24} Corr.* dps./mg. Na
Urine I	1.2	1.62	5	8.1	490	43.3	5.35

* Corrected for counter efficiency of 0.15.



Case 7. No blood counts had been done before the accident.

Medical Findings on Admission to Hospital

The patient was a well developed, athletic appearing young man. The lungs and abdomen appeared normal. A presystolic murmur was heard at the apex. The heart was not enlarged and the rhythm was regular. The skin was clear, without lesions of any sort. The temperature, pulse, respiratory rate and blood pressure were normal. The patient had no subjective complaint on admission to the hospital.

Course

This patient experienced no symptom and showed no physical evidence of radiation injury. The blood pressure rose to 140/90 mm. Hg during the latter part of the first day. He was hospitalized for a four day observation period and then sent home to rest for two weeks. He showed no erythema, petechia, skin rash or epilation. He noted no intestinal symptom or physical weakness. He did not lose weight. Examination 15 months after the accident revealed no change in his physical condition.

Follow-up

The patient felt well and, when last heard from, was living a normal life 35 months after exposure.

The physical examination 28 months after the accident revealed no significant abnormality except those referable to his rheumatic heart disease. There was no clinical evidence of progression of the cardiac lesion since the initial examination. Complete laboratory studies, including liver and kidney function tests, blood studies, and basal metabolic rate, were normal. The electrocardiogram showed prolonged conduction time.

HEMATOLOGY

No previous blood count had been done on this patient. The quantitative changes in the blood count for the 30 day period following the accident are shown in the accompanying graphs (p. 358). There was a gradual fall in the absolute leukocyte count from 10,000 to less than 8,000 cells per mm.[3] There was no significant change in the lymphocyte count, which remained in the low normal range throughout the period of study. No cytologic change was observed in the supravital preparations of the blood. The neutrophils did not show toxic granules. The fixed blood smears from the third to the thirty-fifth days were not studied.

The sternal marrow specimen, aspirated on the fourth day after exposure, appeared to be quantitatively and qualitatively normal. The differential count follows:

	Per Cent
Leukocytes	
Granulocytes	
Neutrophils	
Segmented	16.0
Band	20.0
Metamyelocytes	30.5
Myelocytes "C"	19.0
Eosinophils	1.0
Basophils	1.0
Lymphocytes, small	8.5
Reticulum cells	2.0
Plasma cells	0.5
Nucleated red blood cells per 200 leukocytes	106.0
Maturation of red blood cells	Normal

The blood counts were followed at Los Alamos at frequent intervals for 18 months after the accident. The total leukocyte count remained between 5,000 to 6,000

cells per mm.[3] The lymphocyte count was about 1,000 cells per mm.[3] There was no definite eosinophilia or monocytosis. The erythrocyte and hemoglobin levels did not change. The platelet count has remained above 500,000 per mm.[3] The percentage of abnormal lymphocytes remained below 20.

Summary

Clinical History

This patient, a 21 year old man, received a dose of mixed total-body radiation estimated to be equivalent to 140 roentgens of soft x-rays and 8.7 roentgens of gamma rays. Except for signs of rheumatic heart disease, the patient's physical condition on admission to the hospital was entirely normal. He experienced no immediate or delayed symptom of any sort. Physical examination more than two years after the accident revealed no essential change in the patient's condition.

Clinical Laboratory Findings

The blood count showed only an initial high normal leukocyte count, which gradually fell to the lower limits of normal. The lymphocyte count remained slightly below normal for the entire 28 month period of study. Since no blood study had been made prior to the accident, it is impossible to say whether there was an early reduction in lymphocyte count. The erythrocyte count and hemoglobin level did not fall. The sternal marrow appeared normal on the fourth day following exposure. The blood clotting time was not altered. Urinalyses, stool examinations and limited chemical studies of the serum sodium, blood chlorides and uric acid revealed no abnormality. The urine coproporphyrin was slightly increased, but there was no increase in the quantity of corticoid-like substance, urobilinogen or amino acids in the urine. There was a detectable amount of radiosodium in the serum and of both radiosodium and radiophosphorus in the urine.

Case 8

Clinical History

This 23 year old man received a dose of total-body radiation believed to have been equivalent to 55 roentgens of soft x-rays and 4.37 roentgens of gamma rays. He was eight feet from the assembly when the accident occurred, and was admitted to the hospital one and one-half hours after exposure.

The past history was not remarkable. The patient had been irregularly exposed to ionizing radiation for a six month period before this accident. These exposures were well below 0.1 roentgen per day. He had worked with some toxic chemicals but at no time showed laboratory evidence of bodily injury.

Medical Findings on Admission to Hospital

The patient was a well developed young man. The pulse rate, temperature and respiratory rate were normal, and the physical signs were within normal limits.

Laboratory Data—Case 8

Blood Chemistry

Days After Exposure	Sodium mEq./l	Chlorides mEq./l	Urea Nitrogen mg. %	Uric Acid mg. %
1 (2 hr.)	140	—	—	—
3	—	70.1	8	3.2

Urinalysis

Days After Exposure	Specific Gravity	Albumin	Microscopic
1	1.010	0	2–3 WBC/HPF
4	1.026	0	3–4 WBC/HPF, mucus, occ. epith. cells

Urine Chemistry

Days After Exposure	Corticoid-Like Fraction Ratios			Coproporphyrin		Urobilinogen	
	a 220/240 mμ	b 240/260 mμ	a/b	μg. %	μg./day	mg. %	mg./day
1 (a.m.)	1.88	0.85	2.21	4.8	72	0.03	0.4
1 (p.m.)	—	—	—	3.1		0.01	
Normal Range	1.5–1.7	0.9–1.1	1.4–1.8	4–9	30–100	trace to 0.2	1–4

Blood Clotting Studies

Clotting and prothrombin time were within normal limits.

Urine Amino Acids*

Day of Illness	Cysteic Acid	Aspartic Acid	Glutamic Acid	Glycine	Taurine	Alanine	Valine	Leucine	Unknown Below Alanine	Unknown Below Valine	Other
6 hr.	0	0.1	0.25	0.25	trace	0.1	trace	trace	0	0	—
Controls 3 cases 8–24 hrs.	0	0	0	0.1–0.25	trace	trace—0.1	trace	trace	0	0	serine—trace alanine—trace arginine—trace—0.1

* Amounts expressed in mg./ml. (approximate concentration).

Neutron-Induced Radioactivity of Serum and Urine

Na^{24} Activity in Serum

Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm. @ t = 0	Na^{24} Corr.* dps.	Na^{24} Corr.* dps./mg. Na
Serum I	1.5	3.28	3	9.84	180	20	2.03

P^{32} Activity in Urine

Sample	Time Taken (hours after exposure)	mg. P/c.c.	c.c. Plated	mg. P Plated	P^{32} cpm. @ t = 0	P^{32} Corr.* dps. @ t = 0	P^{32} Corr.* dps./mg. P
Urine I	2.2	1.32	5	6.60	150	16.7	2.53

* Corrected for counter efficiency of 0.15.

LABORATORY DATA—CASE 8—*Continued*

Na^{24} Activity in Urine

Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm. @ t = 0	Na^{24} Corr.* dps. @ t = 0	Na^{24} Corr.* dps./mg. Na
Urine I	2.2	3.32	6	16.6	500	55.6	3.35

* Corrected for counter efficiency of 0.15.

Neutron-Induced Radioactivity of Body Tissues

Beta radiation from teeth, 30 hours after exposure, 193 cpm. on portable Geiger Unit.

Course

The patient felt entirely well during a four day period of hospitalization. He did not experience nausea, anorexia or diarrhea. His skin did not show erythema or petechiae. After leaving the hospital, he noted no weakness or epilation. The patient's weight did not change. The seminal fluid was not examined. Physical examination three months after exposure showed no abnormality.

Follow-up

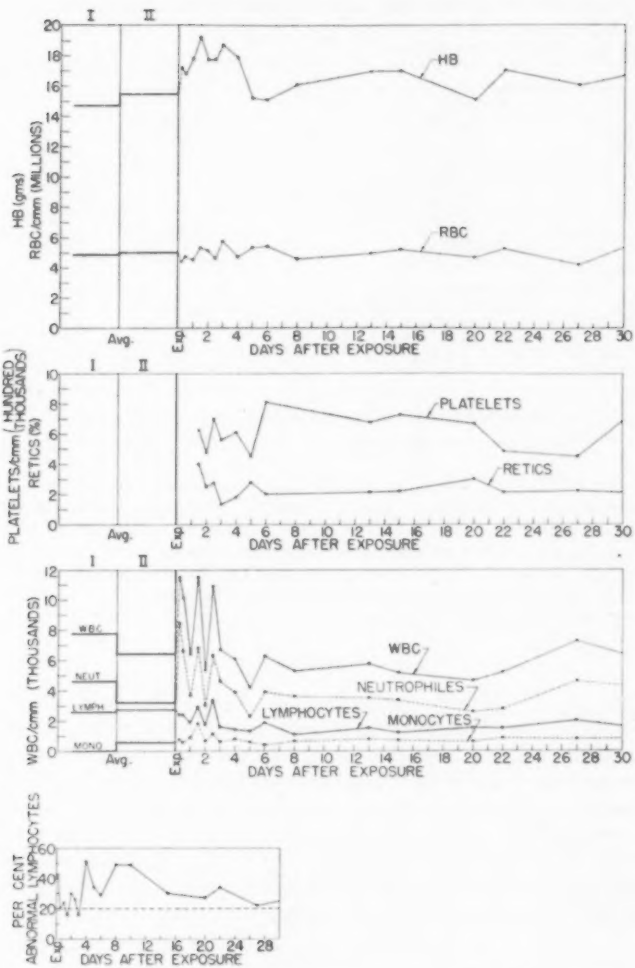
Three and one-half years after exposure the patient's health was good. He had had no serious illnesses since the accident; his weight had not changed significantly. His physical endurance was good, although he was not in such good condition as at the time of the accident, presumably because he now leads a more sedentary life. He was married two and one-half years after the accident. His wife was pregnant at the time of the examination. Physical examination revealed a young man in good physical condition. No abnormality was noted. The lenses of his eyes showed no change. Renal function tests (blood urea nitrogen, phenolsulfonphthalein and concentration) indicated no kidney damage, and the bromsulfalein test of liver function was normal.

HEMATOLOGY

Blood counts prior to the accident showed little variation; the total leukocyte counts ranged from 5,500 to 8,000 cells per $mm.^3$ The lymphocyte level was moderately high.

The quantitative changes in the blood count for 30 days after exposure are shown in the accompanying graphs (p. 363). After an initial period of instability, the leukocyte count fell to 5,000 per $mm.^3$ considerably below the preëxposure level. There was some fall in lymphocytes but not below the normal level; a definite eosinophilia and a probable slight monocytosis occurred. There was no cytologic change in the blood cells. The fixed films from the fourth to the thirtieth days were not examined.

In the three and one-half months that hematologic studies were conducted in the Los Alamos Scientific Laboratory there was little change in the blood count. The total leukocyte count was 5,000 to 6,000 cells per $mm.^3$ The lymphocyte count remained between 1,500 and 2,000 cells per $mm.^3$ slightly below the preëxposure level. The mild eosinophilia (300 to 600 cells per $mm.^3$), which did not exist before exposure, was present immediately following the accident and continuously throughout the entire period of study. There was no change in the red blood cell and platelet counts or in the hemoglobin level.



Case 8. Fourteen counts were done prior to exposure. Four of these were taken in Chicago over a five-month period two years before the accident. The average of these counts is shown in Period I. Ten counts were performed at Los Alamos in the year prior to exposure. The average of these counts is shown in Period II.

A sternal marrow specimen aspirated three and one-half months after the accident was normal grossly and microscopically. The differential count on the supravital preparation of this marrow follows:

	Per Cent
Leukocytes	
Granulocytes	
Neutrophils	
Segmented	6.00
Band	13.75
Metamyelocyte	24.75
Myelocyte "C"	26.50
Myelocyte "B"	1.00
Basophils	0.50
Eosinophils	2.00
Lymphocytes, small	19.50
Clasmatocytes, phagocytic	2.75
Reticulum cells	2.75
Plasma cells	1.00
Megakaryocytes	0.75
	99.75
Nucleated red blood cells per 200 leukocytes	125
Maturation of red blood cells	Normal

Three and one-half years after exposure the blood count was normal. The total leukocyte count was 7,350, with 3,610 neutrophils, 2,140 lymphocytes, 650 monocytes and 810 eosinophils per mm.^{3} The erythrocyte count was 5,960,000 cells per mm.,^{3} with 15.6 gm. of hemoglobin and 2.6 per cent reticulocytes. The platelet count was 941,000 cells per mm.^{3} The formed elements of the blood appeared normal qualitatively. In the 58 lymphocytes seen in supravital preparation, nine contained more than five refractive neutral red bodies.

Summary

This 23 year old man received a dose of total-body radiation estimated to be equivalent to 55 roentgens of 80-kv x-rays and 4.37 roentgens of gamma rays. There was no detectable change in the patient's physical condition and no subjective symptom. The only significant laboratory findings were: (1) an initial granulocytosis and instability in the leukocyte count; (2) a mild eosinophilia; (3) an increase in the number of refractive neutral red bodies in the circulating lymphocytes, and (4) a slight amount of induced radioactivity in the urinary and serum sodium and in the urine phosphorus. There was no significant fall in the erythrocyte count.

Case 9

Clinical History

This 36 year old man was brought to the hospital within an hour of exposure. He was 16 feet from the assembly when the accident occurred. The estimated 42 rem of soft radiation and less than 3 rem of hard radiation that he received were delivered uniformly to his entire body.

His past history was irrelevant. He was married and had two children. He had been exposed to extremely small doses of radiation (much less than 0.1 roentgen per week) over a period of one and one-half years at the Los Alamos Scientific Labora-

Laboratory Data—Case 9

Blood Chemistry

Days After Exposure	Sodium mEq./l	Chlorides mEq./l	Urea Nitrogen mg. %	Uric Acid mg. %
1 (2 hr.)	141	—	—	—
3	—	73.3	14	4.0

Urinalysis

Days After Exposure	Specific Gravity	Albumin	Microscopic
2	1.017	0	Occ. WBC, mucus
3	1.012	0	Occ. RBC

Urine Chemistry

Days After Exposure	Corticoid-Like Fraction Ratios			Coproporphyrin		Urobilinogen	
	a 220/240 mμ	b 240/260 mμ	a/b	μg. %	μg./day	mg. %	mg./day
1 (4 hrs.)	—	—	—	7.5	—	trace	—
2	1.97	1.07	1.84	2.3	—	trace	—
Normal Range	1.5–1.7	0.9–1.1	1.4–1.8	4–9	30–100	trace to 0.2	1–4

Blood Clotting Studies

Clotting and prothrombin time were within normal limits.

Sperm Count

4 months after exposure	50,000,000 per cubic centimeter

Urine Amino Acids*

Day of Illness	Cysteic Acid	Aspartic Acid	Glutamic Acid	Glycine	Taurine	Alanine	Valine	Leucine	Unknown Below Alanine	Unknown Below Valine	Other
6 hr.	0	0	0	0	0.25	0	0	0	0	0	—
1	0	0	trace	0.5	0.25	trace	0.1	0	0	0	—
Controls 3 cases 8–24 hrs.	0	0	0	0.1–0.25	trace	trace—0.1	trace	trace	0	0	serine—trace alanine—trace arginine—trace—0.1

* Amounts expressed in mg./ml. (approximate concentration).

Neutron Induced Radioactivity of Serum and Urine

Na^{24} Activity in Serum

Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm. @ t = 0	Na^{24} Corr.* dps.	Na^{24} Corr.* dps./mg. Na
Serum I	2.0	3.24	3	9.72	135	15	1.52

* Corrected for counter efficiency of 0.15.

LABORATORY DATA—CASE 9—*Continued*

P^{32} Activity in Urine

Sample	Time Taken (hours after exposure)	mg. P/c.c.	c.c. Plated	mg. P Plated	P^{32} cpm. @ t = 0	P^{32} Corr.* dps. @ t = 0	P^{32} Corr.* dps./mg. P
Urine I	1.2	1.12	5	5.60	70	7.8	1.4

Na^{24} Activity in Urine

Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm. @ t = 0	Na^{24} Corr.* dps. @ t = 0	Na^{24} Corr.* dps./mg. Na
Urine I	1.2	2.79	5	13.9	240	26.7	1.92

* Corrected for counter efficiency of 0.15.

tory. Before the war he had worked with a cyclotron but had received what is believed to be little radiation exposure. He had not been exposed to ionizing radiation of any kind for six months prior to the accident. Blood counts and urinalyses had always been normal.

Medical Findings on Admission to Hospital

Examination of the patient revealed no physical abnormality. The exposed portions of his skin were sunburned. The temperature and pulse were normal. The blood pressure was 120/82 mm. Hg.

Course

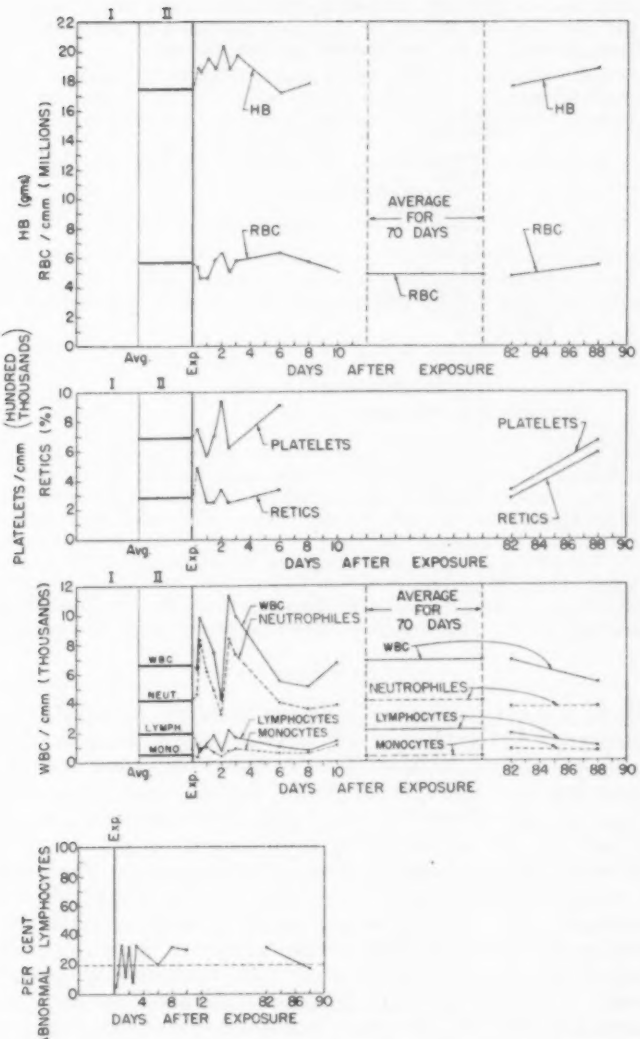
The patient had no complaint on admission to the hospital. He felt slightly nauseated several hours after the accident but ascribed this symptom to nervousness and apprehension. His blood pressure on the day following the accident was 108/72 mm. Hg. He had no other subjective complaint during the four day period of hospitalization or thereafter. His temperature varied between 97° and 99.5° F. during his hospital stay. He noted no weakness, fatigability or gastrointestinal symptom. There was no evidence of erythema or epilation. About two weeks after exposure the patient took a strenuous plane trip without ill effects. He has remained well since that time.

Follow-up

The patient was well and leading a normal life 35 months after exposure. Examination showed no physical abnormality. Complete laboratory studies revealed no variation from normal. His endurance as revealed by the Index of Fitness for Hard Work was 90, which is good for a man of his age and physical condition.

HEMATOLOGY

The quantitative changes in the blood count for the 90 day period after exposure are shown in the accompanying graphs (p. 367). The five blood counts between the twelfth and eightieth days were not done at the Los Alamos Scientific Laboratory. After the initial period of instability of the total leukocyte and granulocyte counts, the blood count remained normal, with no evidence of leukopenia. The lymphocyte count fell slightly and there was a temporary rise in the monocyte level. No cytologic change was observed.



Case 9. Sixteen blood counts were done in the two years before exposure at the Los Alamos Scientific Laboratory. The average of these counts is shown in Period II.

A bone marrow specimen obtained by aspiration of the sternal cavity on the fourth day after exposure showed no significant qualitative or quantitative change. The differential count on the bone marrow specimen follows:

	Per Cent
Leukocytes	
Granulocytes	
Neutrophils	
Segmented	9.5
Band	14.5
Metamyelocytes	30.0
Myelocyte "C"	23.0
Myelocyte "B"	2.5
Eosinophils	2.5
Lymphocytes	11.0
Clasmatocytes, phagocytic	0.5
Reticulum cells	4.5
Plasma cells	0.5
	98.5
Nucleated red blood cells per 200 leukocytes	87
Maturation of red blood cells	Normal

Since the last count indicated on the chart, the leukocyte count as determined in the Los Alamos Scientific Laboratory has been stable, ranging from 4,500 to 8,600 cells per mm.,[3] which is slightly below the preëxposure level. The average eosinophil count before exposure was 325 cells per mm.[3] This value varied between 400 to 800 for 14 months after the accident. Recent eosinophil counts have been below 300 cells per mm.[3] The platelet and erythrocyte counts and the hemoglobin level did not change significantly. About 20 per cent of the lymphocytes were abnormal in refractive body content for 10 months after the accident. Since this time, very few abnormal lymphocytes have been found. The blood count 38 months after exposure was not abnormal.

Summary

This 36 year old man received a dose of total-body radiation believed to be equivalent to 42 roentgens of soft x-rays and 2.72 roentgens of gamma rays. He experienced no symptom other than mild nausea several hours after exposure, and developed no clinical sign of injury. The leukocyte count was high and unstable for several days after exposure. There was no lymphopenia, but the eosinophils increased moderately and the number of neutral red bodies in the lymphocytes was slightly elevated. The reticulocyte count increased several months after exposure when the patient returned to Los Alamos after spending several months at sea level. There was no abnormality observed in the urine or stool samples or in the limited number of chemical determinations on the blood. The blood-clotting time was not increased, and the amount of amino acids in the urine was not abnormal. The urinary corticoid-like substance, coproporphyrin and urobilinogen were not increased in amount. There were detectable amounts of radioactivity in the serum and urine sodium and in the urine phosphorus. The sperm count was within the limits of normal four months after exposure. The patient was well and in good physical condition 38 months after exposure. The Index of Fitness for Hard Work test at that time showed a score of 90.

Case 10

Clinical History

This 23 year old unmarried man was 16 feet from the assembly. His back was turned to the critical assembly at the time of exposure. The dose of radiation delivered to his entire body was estimated to have been equivalent to 33 roentgens of soft x-rays and 2.41 roentgens of gamma rays.

The past, social and family history was irrelevant. He had not been exposed previously to ionizing radiation or to toxic chemicals.

Medical Findings on Admission to Hospital

Examination on admission to the hospital revealed a young man in good physical condition. He was sunburned and his face and shoulders showed many fresh lesions and old scars of acne vulgaris. His blood pressure, temperature and pulse were normal.

He noted no unusual symptom on admission to the hospital.

Laboratory Data—Case 10

Urinalysis

Days After Exposure	Specific Gravity	Albumin	Microscopic
2	1.010	0	Mucus
3	1.022	0	Mucus, occ. WBC

Blood Chemistry

Days After Exposure	Sodium mEq./l	Chlorides mEq./l	Urea Nitrogen mg. %	Uric Acid mg. %
1 (1½ hrs.)	141	—	—	—
3	—	67.8	8	3.1

Urine Chemistry

Days After Exposure	Corticoid-Like Fraction Ratios			Coproporphyrin		Urobilinogen	
	a 220/240 mμ	b 240/260 mμ	a/b	μg. %	μg./day	mg. %	mg./day
1 (4 hrs.)	—	—	—	3.2	—	trace	—
2	1.88	1.08	1.74	1.9	24	trace	—
Normal Range	1.5–1.7	0.9–1.1	1.4–1.8	4–9	30–100	trace to 0.2	1–4

Urine Amino Acids*

Day of Illness	Cysteic Acid	Aspartic Acid	Glutamic Acid	Glycine	Taurine	Alanine	Valine	Leucine	Unknown Below Alanine	Unknown Below Valine	Other
6 hr.	0	0	0	0	0	0	0	0	0	0	—
1	trace	0	0	0	0.25	0	trace	0	0	0	—
Controls 3 cases 8–24 hrs.	0	0	0	0.1–0.25	trace	trace—0.1	trace	trace	0	0	serine—trace alanine—trace arginine—trace—0.1

* Amounts expressed in mg./ml. (approximate concentration).

LABORATORY DATA—CASE 10—*Continued*

Neutron-Induced Radioactivity of Serum and Urine

Na^{24} Activity in Serum

Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm. @ t = 0	Na^{24} Corr.* dps.	Na^{24} Corr.* dps./mg. Na
Serum I	1.4	3.18	3	9.54	110	12.2	1.22

P^{32} Activity in Urine

Sample	Time Taken (hours after exposure)	mg. P/c.c.	c.c. Plated	mg. P Plated	P^{32} cpm. @ t = 0	P^{32} Corr.* dps. @ t = 0	P^{32} Corr.* dps./mg. P
Urine I	2.2	1.12	5	5.60	70	7.8	1.4

Na^{24} Activity in Urine

Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm. @ t = 0	Na^{24} Corr.* dps. @ t = 0	Na^{24} Corr.* dps./mg. Na
Urine I	2.2	2.98	5	14.9	170	18.9	1.27

* Corrected for counter efficiency of 0.15.

Neutron-Induced Radioactivity of Body Tissues

Beta radiation from teeth, 30 hours after exposure, *Bkg.* on portable Geiger Unit

Course

The patient felt well during the four day observation period in the hospital. There was no change in blood pressure, temperature, pulse or respiratory rate. His appetite was good and he experienced no gastrointestinal symptom. He returned to work after discharge from the hospital with explicit instructions to avoid further exposure to radiation. He noted no weakness on resuming physical activity. There was no epilation and no change in the condition of his skin. Studies on spermatogenesis were not done. He did not lose weight after the accident. Examination four months after exposure indicated no change in the patient's physical condition.

Examination of the patient 10 months later revealed no abnormality. His weight and the condition of his skin were unchanged. He felt well except for recurrent attacks of sinusitis.

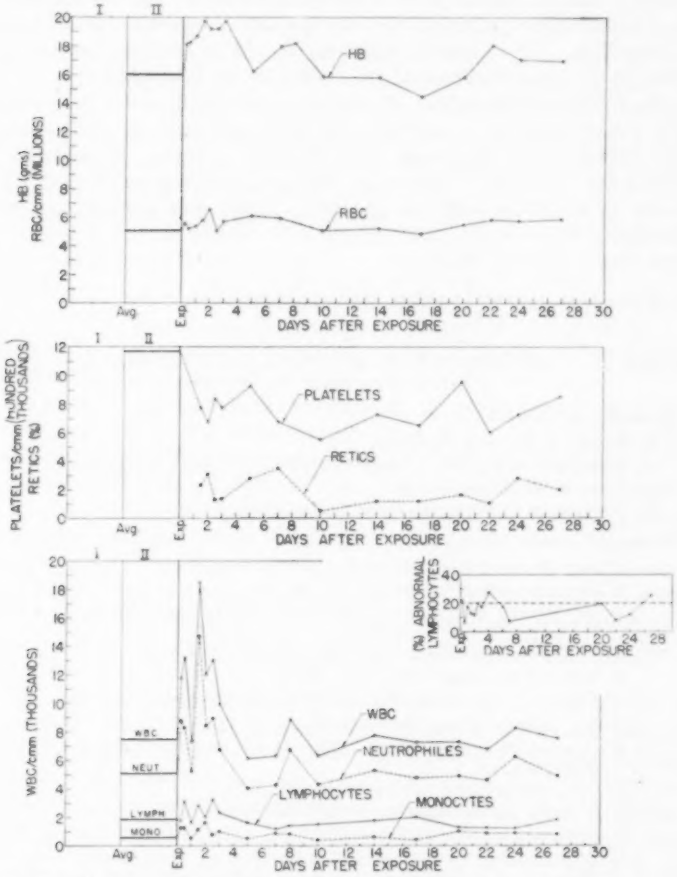
Follow-up

Forty-one months after exposure, the patient was in excellent health and had no complaint. A complete physical examination revealed no unusual physical finding except moderately severe acne. Laboratory studies, including a complete blood count, liver and kidney function tests, and blood chemistry studies were within normal limits.

HEMATOLOGY

Blood counts prior to the accident had always been normal. The changes in blood count during the month after exposure are shown in accompanying graphs (p. 371). The leukocyte count has not shown significant fluctuation since the initial marked leukocytosis. Neither leukopenia nor lymphopenia occurred. There was no

significant change following the last count shown on the chart during the three month period in which the blood was studied in the Los Alamos Scientific Laboratory. The platelet count did not fall. There was no anemia or eosinophilia but there was a slight monocytosis. The leukocytes showed no cytologic change in either supravital or fixed preparations. A bone marrow specimen was not obtained.



Case 10. Four blood counts were taken in the 18-month period prior to exposure. The average of these counts is shown in Period II.

Repeated blood counts between the second and third years after exposure revealed a constant high normal white blood count ranging between 8,300 and 11,100 cells per mm.^{3} The hemogram, the erythrocyte and hemoglobin levels, the platelet and reticulocyte counts, and the clotting and bleeding times were within normal limits.

Summary

This 23 year old man received a dose of total-body radiation estimated to be equivalent to 33 roentgens of soft roentgen-rays and 2.41 roentgens of gamma rays. He experienced no symptom and showed no sign of injury. Physical examination three years after the accident revealed no abnormality. The only abnormality in leukocyte count consisted of an initial granulocytosis and instability. There was no lymphopenia and no constant increase above normal in the refractive neutral red bodies in the lymphocytes. The erythrocyte count and hemoglobin showed an early rise, followed by a decrease to the preëxposure level. Urinalyses, stool examinations, serum sodium, blood chloride, uric acid and urea nitrogen were not abnormal. The corticoid-like substances in the urine, the urinary coproporphyrin, urobilinogen and amino acids were not elevated. There was a slight amount of radioactivity in the serum and urine sodium and in the urine phosphorus. Sperm counts were not obtained.

Section IV. The Biologic Basis for the Clinical Response Seen in the Acute Radiation Syndrome.

A. Physical Considerations
   1. Nature of Ionizing Radiation
   2. Relative Biologic Effectiveness (R.B.E.) of Ionizing Radiations
   3. Units of Radiation Dosage
   4. Penetration of Matter by Ionizing Radiation

B. Biological Considerations
   1. Cellular Damage Produced by Ionizing Radiation
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      b. Mechanisms by which radiochemical changes cause cell injury and death
         1. Inactivation of enzymes
         2. Modification of genes and chromosomes
      c. Types of radiation-induced cell death
      d. Effect of radiation on the cell environment
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         1. Latent period preceding tissue damage
         2. Other factors influencing tissue damage
      b. Variation in tissue radiosensitivity
      c. Regeneration of radiation-injured tissue
      d. Contrast of radiation-induced tissue damage with that caused by other toxic agents
   3. Systemic or Constitutional Response of the Irradiated Individual
      a. Toxic products given off by damaged tissue
      b. Disturbances in organ function produced by radiation
      c. Factors secondary to organ damage in radiation injury
      d. Response of the individual to total-body irradiation
   4. Variation in the Response of the Individual to Total Body-Irradiation

C. Summary

IV. The Biologic Basis for the Clinical Response Seen in the Acute Radiation Syndrome

The pathogenesis of the acute radiation syndrome can be appreciated more completely if one understands the way in which ionizing radiations produce biologic damage. Therefore, before discussing the medical aspects of this disease, a brief résumé of some of the pertinent fundamental facts and concepts underlying the biologic actions of radiation will be presented. Only those phases of the subject that relate to the present study are discussed in this section. The reader is referred to the book by Lea (1947), to the group of articles published in the British Medical Bulletin (Spear, 1946; Gray, 1946; Catchside, 1946), and to an article by Zirkle (1949) for a more thorough discussion of the actions of radiation on tissue.*

A. *Physical Considerations*

Since this report is written primarily for the physician, it seems worthwhile to define the more important physical terms and to explain their significance as well as the limits of their application to biology.

1. *Nature of Ionizing Radiation*

The radiations of interest in this study are neutrons, gamma rays, x-rays and beta particles. These radiations have in common the property of dissipating energy in matter by causing ionization of atoms. Ionization, in this sense, means the ejection of an electron from its mother atom or molecule, with the resultant production of two ions, one being the negatively charged electron, the other the positively charged residual atom or molecule. The electron usually comes to rest at some distance (perhaps 50 to 100 microns in wet tissue) from the positive ion. This separation makes a re-combination of the two ions impossible. The ion pair then exists for a fraction of a minute before being neutralized by coming into contact with other ions of opposite charge.

The amount of energy expended by radiation in producing an ion pair is inconstant, because an electron can be ejected from its atomic orbit with varying degrees of violence. Also, many instances of incomplete separation of the electron from the atom are known to occur. Such incomplete removal is known as excitation of the atom (or molecule). Taking excitation along with ionization into account, it has been found that the average amount of energy expended for every ion pair produced in air or in tissue is about 32.5 electron-volts. Assuming that all of its energy is dissipated by causing ionization or excitation, a single gamma ray or a beta particle having an energy of 1,000,000 electron volts will produce 30,785 ion pairs before dissipating all its energy in tissue.

* In most instances in this as well as in succeeding sections, reference is made to recent review articles rather than to individual papers.

The ability of ionizing radiation to produce ion pairs distinguishes it from other types of radiation, such as visible light and near ultra-violet rays, which lose their energy in tissue largely by the excitation of atoms and molecules. The ionization caused by the radiations with which we are concerned is of utmost practical importance for two reasons: first, the ionization of tissue is sometimes said to be responsible for all of the biologic effects of the radiation * (Lea, 1947), and, second, the ionization of air or tissue forms the basis for measurement of the radiation dose.

2. Relative Biologic Effectiveness (R.B.E.) of Ionizing Radiations

All forms of ionizing radiation produce the same type of tissue reaction. However, the efficiency in producing the reaction varies with the nature of the radiation, even though the observed final effects are essentially the same. For example, neutrons will cause more damage per unit energy absorbed in the tissue than will an identical amount of energy dissipated by gamma rays or x-rays. The difference in biologic effectiveness of these radiations is due to the spatial distribution of the ions produced along the tracks of individual particles or photons. In general, the efficiency of a radiation in causing biologic damage can be correlated with the density of the ions it produces (Zirkle, 1935). For example, fast neutrons, which cause ionization in an indirect manner described in Section VIII, produce dense clusters of ions, while gamma rays produce relatively widely scattered ion pairs. Therefore, fast neutrons are more effective in causing biologic damage than are gamma rays, but they are not so damaging as alpha particles from radium, which cause even denser ion tracks (Zirkle, 1935).

The term *relative biologic effectiveness* (R.B.E.) has been introduced to take into account the quantitative difference in the biologic action of ionizing radiation per unit of energy absorbed (Zirkle, 1943). The R.B.E. is a convenient term for use in comparing damage produced by different radiations. For example, in most acute reactions in mammalian tissues, the R.B.E. of fast neutrons as compared to gamma rays has been reported to be between four and 10 (Gray et al., 1940; Evans, R. D., 1947); in cases of chronic exposure to the two radiations, the R.B.E. is even higher. In the former comparison it is meant that one unit of energy of fast neutrons will produce the same biologic effect as four to 10 units of gamma rays, the units of energy being those actually absorbed in the tissue. It must be emphasized that the R.B.E. determined for a single biologic effect does not hold for all tissue reactions. Thus, the R.B.E. for fast neutrons and gamma rays is not a constant, but differs for different measured effects in a single tissue, and even for the same effect in different tissues of the same individual. This means that it is not feasible to use a single value for the R.B.E. to cover all biologic effects seen in animals exposed to two different radiations.

* Recently, it has been shown that in certain radiochemical reactions as exemplified by the dissociation of organic chlorides, excitation plays a more important rôle than ionization (H. A. Andrews, personal communication). It seems possible that reactions of this type, although as yet undemonstrated, may take place in irradiated protoplasm. (See also Gray, 1947.)

Despite differences in effectiveness, and in some cases in the mechanism of producing tissue damage (see Sections VIII and X), the biologic actions of the different types of ionizing radiations are sometimes directly additive. Thus, if an animal receives half of a lethal dose of fast neutrons and half of a lethal dose of gamma rays, death will occur in the same manner as if a lethal dose of either radiation had been given singly (Zirkle et al., 1945). There are other experiments, however, which indicate that sometimes the actions of the combined radiations can be less effective than either applied alone (Mitchell, 1947-b).

3. *Units of Radiation Dosage*

The units of ionizing radiation in common usage are the roentgen, the roentgen equivalent physical (rep), the roentgen equivalent man (rem), and the gram-roentgen.* As stated above, the ionization of air or tissue forms the basis for measurements of radiation dose. The units of dose are defined in terms of numbers of ions produced per cubic centimeter of air under standard conditions or per gram of aqueous tissue. Since the amount of ionization depends upon the energy dissipated by the radiation, the radiation dose may also be expressed in terms of the energy loss per unit mass of air or tissue. This latter designation is particularly convenient for use in dose computations.

A *roentgen* of x-rays is that amount which will produce 2.08×10^9 ion pairs in a cubic centimeter of air under standard conditions of temperature and pressure. It may also be defined as that amount of radiation which dissipates 83.8 ergs per gram of dry air. It is important to realize that this term does *not* refer to the rate at which the radiation is administered or to the amount of tissue exposed to the x-ray beam.

Since, strictly speaking, the roentgen can be used only for measuring x-rays and gamma rays, other units have been formulated to describe doses of beta rays, neutrons and other types of radiation. Of these, the *roentgen equivalent physical*, or *rep*, perhaps the unit most frequently used in America, was until recently based on the ionization of air. The *rep* was formerly defined as that amount of any ionizing radiation (beta rays, neutrons, etc.) which produces the same number of ion pairs per gram of air (or which dissipates the same amount of energy per gram of air, namely, 83.8 ergs) as one roentgen of x-rays or gamma rays. Now, however, the definition of the rep has been modified so that it refers to the energy dissipated in a gram of aqueous tissue rather than in air (Parker, 1950).† As has been pointed

* The n unit, an empiric unit of neutron dosage frequently seen in the radiobiologic literature, is based on measurements using a certain type of commercially available ionization chamber. It is defined as the neutron dose, which gives the same reading in a Victoreen Thimble Chamber as 1 roentgen of gamma rays from radium. The value of the n differs slightly for 25- and 100-roentgen chambers.

† The energy dissipated by a given radiation is not the same in air and tissue. The difference in energy adsorption is particularly marked in the case of neutrons, for reasons that will become obvious in Section VIII, when the mode of interaction of neutrons and matter is discussed. Lesser differences in energy transfer also occur in the case of electromagnetic radiation absorbed in air and tissue. Thus, the energy loss by one roentgen of hard x-rays is 83.8 ergs per gram of air and 93 ergs per gram of wet tissue. This difference must be taken into consideration in dose computations.

out, the biologic efficacy for a given amount of ionization varies with the type of radiation. In an attempt to take the relative biologic effectiveness into consideration so that doses of different kinds of radiation can be compared directly, the term *roentgen equivalent man*, or *rem*, has been introduced. A *rem* of any type of radiation—neutrons, for example—is defined as that amount which is equivalent in its biologic action on tissue to 1 roentgen of hard x-rays. This value for any type of radiation can be computed by multiplying *reps* by value of the R.B.E. of the radiation compared to hard x-rays.

Since the terms roentgen, rep and rem do not take into account the amount of tissue which has been irradiated, the *gram-roentgen*, another radiation dose unit, has appeared (Mayneord, 1940; Evans, 1947). One gram-roentgen is defined as the energy lost in 1 gm. of air by one rep of ionizing radiation or 83.8 ergs. In dose calculations, this unit is sometimes used to integrate the total energy dissipated in a mass or volume of tissue; the radiation dose so derived is called the *integral* or *volume dose*. In such an application, the integral dose is the product of the radiation dose in energy units multiplied by the mass of irradiated tissue in grams. This means that the same integral dose is delivered whether 100 gm. of tissue are irradiated with 1 roentgen or 1 gm. is exposed to 100 roentgens. It turns out that the amount of energy lost by radiation in passing through the human body is usually large compared to the gram-roentgen. Therefore, the term "megagram-roentgen" is often used in practice when this unit is applied to measurements in man.

4. *Penetration of Matter by Ionizing Radiation*

Ionizing radiations differ in their ability to penetrate tissue. Fast neutrons, energetic gamma rays and hard x-rays have great powers of penetration. Thus, radiation of this type originating from a source outside the body has the potentiality of reaching and injuring all of the organs in the body. Neutrons, however, are less penetrating in aqueous tissue than are x-rays or gamma rays of the same energy. Soft x-rays are also considerably less penetrating in tissue than are hard x-rays or gamma rays. The range of beta rays in tissue, in contrast to that of the penetrating radiations, is not more than 2 to 4 mm. Thus, beta rays from a source outside the body can injure only the skin and skin appendages. The effect of beta rays from radioactive materials deposited inside the body is similarly confined to the cells in the immediate vicinity of the radioactivity.

The term "depth dose" is frequently used to describe the penetrating power in tissue of a beam of radiation which originates outside the body. It refers to the fraction of the radiation dose which reaches a given point within the body, and is usually expressed in terms of the per cent of the dose at the body surface. The depth dose depends upon the type and energy of the radiation and the size of the beam. This term is particularly useful in the radiation therapy of internally placed tumors.

B. *Biologic Considerations*

In order to translate the physical phenomenon of ionization into the ultimate clinical picture of the acute radiation syndrome, it is necessary to consider each stage in the sequence of events leading to the response of the body as a whole. Thus, the biochemical changes induced by ionizing radiation in protoplasm must be viewed at the level of cellular activity; similarly, the reaction of injured tissues should be evaluated in terms of damage to the component cells; and, finally, the clinical response of the individual can be appreciated only when the damage to each organ system is taken into account.

In discussing the fundamental biologic reactions, it will be noted that conclusions concerning radiation effects in man are drawn from observations on numerous biologic materials, ranging from simple unicellular organisms to complex tissues of other animal species. The tendency to oversimplify biologic mechanisms and to explain all observed phenomena in terms of those mechanisms which we understand is obvious. The extrapolation of diverse data to man and the oversimplification of cell mechanisms serve a purpose, since they provide stepping-stones to a working concept of the nature of the acute radiation syndrome.

1. *Cellular Damage Produced by Ionizing Radiation*

The fundamental lesion in the irradiated individual is damage to the cell. The cytogenetic response of individual irradiated cells is incompletely understood, but discussion of experimental observations and of the present concepts of the mechanism of cell damage can add to our understanding of the biologic response in man.

a. *Radiation-induced chemical changes*

Irradiation of cells or tissues leads to chemical changes in the molecules which have been ionized. The chemical reactions that occur in protoplasm are of two general types, depending upon the character of molecule which has been affected. Thus, there may be radiochemical changes due to ionization of either molecules of protoplasm or water molecules (discussed by Lea, 1947). In the first instance, a molecule which has been ionized may undergo either chemical modification or disruption. For example, a protein molecule may be denatured or broken into smaller peptide units as a result of ionization. It is easy to see how such a biochemical change may lead to cell injury, particularly if the affected molecules are important to the function of the cell. In the second type of chemical change, that involving water molecules, it is believed that ionized water molecules may undergo a series of chemical transformations which can result in the formation of highly reactive radicals or compounds. For example, there is indirect evidence that ionized water molecules may be converted into uncharged hydroxyl radicals (OH), atomic hydrogen (H), hydrogen peroxide (H_2O_2) and hydroperoxide (O_2H) (Lea, 1947). It has been suggested recently that irradiation of water containing organic material also leads to the formation of more stable organic peroxides (Barron, Flood, Gasvoda, 1949). These

"activated" products formed in the aqueous medium of protoplasm can react with organic constituents of the cell, and this provides an indirect mechanism whereby cell damage can be produced.

The primary radiochemical reactions in irradiated aqueous media are limited quantitatively by the number of atoms which have been ionized. Usually one or not more than two or three molecules undergo a chemical change for every ion produced (Lea, 1947). In some organic compounds, the yield of chemical reactions is much lower than this. Since ionization occurs randomly throughout protoplasm, it may be calculated that two or three ionizations and subsequent chemical changes occur in the aqueous medium for every one in the constituent molecules of protoplasm. It is impossible to say at present which of these two types of radiochemical reaction, i.e., that in water or in protoplasmic molecules, is more important biologically. Undoubtedly, many of the organic molecules, modified directly by irradiation, are unimportant to immediate cellular function, and a change in their chemical nature does not interfere with normal cellular activity. In the case of the formation of activated products of irradiated water, the loss of individual water molecules per se does not affect the cell directly. However, labile groups of nearby molecules compete for the highly reactive water products which, being small, can move easily in protoplasm and act over large molecular distances. It seems likely that the most labile of the chemical groups in the protoplasm will attract the activated products and undergo more chemical reactions than will less labile groups. For example, it has been shown that sulfhydryl groups of a certain kind are particularly prone to be oxidized in this manner (Barron and Dickman, 1949; Barron et al., 1949). Thus, there would seem to be a certain degree of selectivity in radiochemical reactions in protoplasm, although not in the same sense as occurs in ultraviolet radiation, which is selectively absorbed by specific molecular groups.

b. *Mechanisms by which radiochemical changes cause cell injury and death*

When living tissue is exposed to penetrating radiation, such as the 1.3 million volt gamma rays from radioactive cobalt or the gamma rays from radium, which have an average energy of 0.7 million volts, energy is absorbed fairly uniformly throughout the tissue mass. Ion pairs are produced at the rate of about 1.8 ion pairs per cubic micron of tissue per roentgen. A nominal tissue cell having a volume of 500 cubic microns will have formed in it about 900 ion pairs for every roentgen.

Thus, it becomes obvious that the amount of energy which produces lethal effects in cells is exceedingly small. For example, 400 roentgens of x-rays, which will cause serious or possibly fatal radiation injury in man, produce approximately 360,000 ion pairs in a cell having a volume of 500 cubic microns. The amount of energy responsible for this ionization is less than one millionth of the energy expended by the cell in aerobic and anaerobic metabolism during the course of 24 hours of normal life. The

small amounts of energy involved and the consequent small number of ion pairs formed mean that only a very small fraction of all of the molecules in a cell will be affected even after exposure to large doses of radiation. It has been estimated that a dose of 1,000 roentgens of x-rays modifies only one in 10,000,000 molecules in a cell of average size (Zirkle, 1949). These considerations make one realize that the primary radiochemical changes which occur randomly among a relatively few molecules must be greatly amplified by intracellular processes to account for the visible structural changes seen under the microscope in radiation-injured tissues. Although there may be other methods of amplification of primary radiation effects, the following two mechanisms have been observed experimentally: (1) inactivation of enzyme molecules, and (2) modification of key genetic units within the cell nucleus.

(1) *Inactivation of enzymes:* Inactivation of a single enzyme molecule by radiation may influence many thousands of other molecules in the reaction system. This can be illustrated by the accumulation of ribonucleic acid in the cytoplasm of irradiated cells, as demonstrated by ultraviolet photomicrography (Mitchell, 1942). It has been calculated that at least 1,000 to 100,000 nucleic acid molecules are indirectly affected for every molecule directly ionized by radiation (Mitchell, 1943, 1946). The actual amplification must be much greater than this, since only relatively few of the molecules directly modified by the radiation are concerned with nucleic acid metabolism. It seems obvious that this effect on nucleic acid metabolism must be mediated through damage to enzyme systems. This has been confirmed by the observation that irradiation of rats diminished the ribonuclease activity in the spleen (Carter, 1949). Further and more direct proof of the action of radiation on intracellular enzymes is shown by the selective inhibition of sulfhydryl oxidative enzymes in various tissues demonstrable after exposure of an animal to 100 roentgens or more of x-rays (Barron, Wolkewitz and Muntz, 1947).*

(2) *Modification of genes and chromosomes:* A far more effective method of amplifying primary radiation effects is through destruction or modification of key intranuclear molecules which control important cellular processes. Two main types of such intranuclear changes have been shown to be responsible for severe damage or death of cells. The first, and possibly the simplest, is the gene mutation. A mutation of this sort can be produced by a single ionization or, at the most, a cluster of two or three ionizations within a gene unit (Lea, 1947). The yield of mutations is directly proportional to the dose for single doses greater than about 1 roentgen. For very low doses, much less than 1 roentgen, the experimental data

* Indirect experimental evidence suggests that the effect of radiation on the easily damaged -SH enzymes results from the inactivation of the molecule by "activated" water (Barron and Dickman, 1949-a). The effect of radiation on the more resistant non-SH containing enzymes is believed to be a result of denaturation of the enzyme molecule. The great radiosensitivity of the former type of compound is shown by the fact that significant inhibition of adenosine triphosphatase can be achieved by irradiation of a pure solution of the enzyme with *one* roentgen of x-rays (Barron et al., 1949-b).

do not indicate a strict proportionality (Evans, 1949; compare, however, Muller, 1950). The second type of intranuclear damage is due to the production of structural changes in chromosomes. Breakage of chromosomes may occur if an ionizing particle passes through a chromosome or in its immediate vicinity (Lea, 1947).* As few as 20 ionizations within a chromosome may be sufficient to cause a chromosome break (Gray, 1946). The number of simple chromosome breaks, like the yield of gene mutations, is directly proportional to the dose for large doses of the magnitude associated with the acute radiation syndrome. It has been estimated that 2,048 roentgens of x-rays would be required to cause an average of one break per chromosome in irradiated grasshopper neuroblast cells (Carlson, 1941). Most chromosome breaks are restituted, but persistence of the fragments or abnormal structural rearrangements occur frequently. Chromosomal abnormalities can be visualized easily during mitosis, when the chromosomes become large and readily stainable. Examples of bizarre chromosomal aberrations can be seen in the photomicrographs of lymphoid and intestinal tissues of the fatally injured patients of the present series. (See photomicrographs, Appendix I.)

Gene mutations and structural changes of chromosomes can lead to death of the cell. Lethal gene mutations have been convincingly demonstrated in bacteria and viruses (Lea, 1947). Recessive lethal gene mutations (which may not become manifest for many generations) also have been observed in fruit flies (*Drosophila melanogaster*) (Lea, 1947). In irradiated mammals there are relatively few rigidly proved examples of experimentally produced gene mutations in germ plasm (Hertwig, 1939; Charles, 1949). In contrast to lethal gene mutations, which can be easily demonstrated in lower organisms but not in higher animals, chromosomal aberrations (or chromosome mutations, as they are sometimes called if mitosis is successful) have been shown to be an important cause, if not one of the primary causes, of cell death in many biologic materials, including mammalian tissues (Lea, 1947). Chromosomal aberrations, such as the failure of a broken chromosome to restitute, or the formation of chromosomal bridges, may render a cell incapable of dividing for obvious mechanical reasons. Presumably, this type of chromosomal damage is responsible for the delayed type of cell death which occurs during mitosis, discussed later in more detail. Even though a cell with chromosomal structural changes may

* The concept that ionization occurring within a specific and often submicroscopic portion of a cell leads to cytogenetic change of a definite type is known as the "target theory" (Lea, 1947). This theory has been used for some time to explain the quantitative aspects of radiation-induced gene mutations and chromosome breaks. The comparatively recent demonstration that chemicals such as the nitrogen mustards can also produce mutations and chromosome breaks makes it clear that other mechanisms besides that implied in the target theory may play a rôle in the production of radiation-induced cytogenetic changes (Zirkle, 1949). One of the other obvious mechanisms is that mediated through "activated" water. It has been stated recently that the target theory is encountering more and more difficulty in explaining radiation effects even in relatively stable biologic systems (Koller, 1949). It is evident from the opinions expressed in the current literature that increasing emphasis is being placed on indirect or radiochemical mechanisms as a cause of cytogenetic effects in irradiated tissues.

complete mitosis successfully, the genetic imbalance in the daughter cells may be incompatible with life or continued reproduction.*

c. *Types of radiation-induced cell death*

Overlooking, for the moment, indirect cell death due to radiation effects on the cell environment, it appears that there are two main types of direct radiation-induced cell death. The first is observed in cells in the resting, or intermitotic, stage. This mode of death occurs soon after exposure and is caused only by large radiation doses. The exact mechanism responsible for prompt cell death is not clear, but it seems likely that it is due to disruption of enzyme systems. Histologically, this type of cell death is similar to the nonspecific cytolysis seen in other pathologic conditions. The second kind of death does not occur until the fatally injured cells attempt mitotic division. Such delayed cell death, produced by relatively small doses of radiation, is probably due to chromosomal damage (Lea, 1947). Cell death during mitosis is encountered rarely, if ever, except in tissues injured by radiation or mitotic poisons.

The two types of radiation-induced cell death are illustrated by experiments with tissue cultures (Laznitski, 1940, 1943). Exposure of a culture of chick fibroblasts to 2,500 roentgens of x-rays results in the degeneration of a substantial number of resting cells within a few hours. In contrast, irradiation of the tissue cultures with 100 roentgens has no immediate effect on the resting fibroblasts. Later, however, when many of these cells try to divide, they either degenerate during the act of mitosis or produce nonviable daughter cells.

Delayed cell death during or after mitosis can be demonstrated indirectly in vertebrates. Irradiation of an animal (tadpole, mouse, etc.) produces a prompt decrease in the mitotic activity of proliferating tissue (Spear and Glucksmann, 1938; Knowlton and Hempelmann, 1949). This is due to the fact that cells in the premitotic phase are rendered temporarily unable to enter mitosis.† After a lag period, the length of which depends upon the size of the dose of radiation and the nature of the tissue, the cells regain their ability to divide. Careful studies correlating the mitotic activity with cell degeneration after irradiation with a few hundred roentgens of x-rays indicate that, in tadpoles and in the developing rat retina, degeneration of cells does not occur until mitotic activity is resumed (Spear and Glucksmann, 1938; Tansley, Spear and Glucksmann, 1937). There is an excellent cor-

* The consideration of nonlethal gene or chromosome mutations in germ plasm, with transmission of altered characteristics to the offspring of an individual, is beyond the scope of this discussion. The reader is referred to a recent report by Dr. Donald Charles (NEPA, 1949) and to other sources (Glucksmann, 1946) for a consideration of the effect of acute doses of radiation on reproductive tissues. The papers by Evans (1949) and Muller (1950) show the divergent opinions as to the ultimate quantitative effects on future generations of radiation-induced mutations in germ cells.

† The cause of the delay in cell division is not definitely established, but it may be related to the temporary disturbance in the desoxyribonucleic acid metabolism shown to occur in radiation-injured cells (Hevesy, 1945; Lea, 1947). Recently it has been suggested that the suppression of mitosis after irradiation is related to the high sulfhydryl content of dividing cells (Barron and Dickman, 1949-a).

relation between the numbers of mitotic figures and degenerating cells. This is strong circumstantial evidence that the tissue cells do not die until they attempt to divide.

Experimental study also indicates that animal cells are particularly sensitive to the chromosomal type of lethal radiation damage in the stage of mitosis just preceding prophase (Marshak, 1942-a). The premitotic radiosensitivity is not so pronounced with neutron irradiation as with x-rays (Marshak, 1942-b; Spear and Tansley, 1944). This observation, which suggests that the resting cells are more severely damaged by neutrons than by x-rays, is an example of one of the few demonstrable qualitative differences between the biologic actions of these two types of radiations. In contrast to these observations in animal tissues, it has been possible to show that in plant cells (*Trillium*) irradiated with x-rays, chromosomal damage is greatest in the metaphase and anaphase stages of mitosis (Sparrow, 1944). The chromosomal abnormalities so induced do not become manifest until the following cell division. Other experiments with wasp eggs (Whiting, 1945) and with *Tradescantia* also indicate that cells in the late stages of mitosis at the time of irradiation are more susceptible to radiation injury than are cells in prophase. In *Tradescantia*, cells which are irradiated during metaphase suffer about 10 to 15 times as many chromosomal aberrations as do those in prophase and about 30 to 50 times as many as do resting cells (A. D. Conger, personal communication). It is conceivable that, had the animal experiments mentioned above been continued through the second postexposure cycle, cells in other phases of mitosis would also have been found to be more radiosensitive than those in prophase.

d. *Effect of radiation of the cell environment*

Although cellular damage due to intracellular changes is undoubtedly important, recent experiments have shown that the effect of radiation on the environmental media also may contribute to the injury of simple organisms (Evans, T. C., 1947; Dickey, Cleland and Lotz, 1949). In the complex body tissues of mammals, it is likely that the action of radiation on the cellular environment must play an even greater rôle in determining the response of the cell. Thus, damage to its blood supply or the action of toxic products given off by adjacent dead or dying tissue may cause death of the irradiated cell. The dry gangrene and ischemic necrosis of the tissues of the hand of case 1 are examples of cellular death en bloc, due to interruption of its blood supply. The relative importance of direct cellular damage and of environmental changes in producing death of irradiated tissues is not clearly understood for the dose range usually responsible for the acute radiation syndrome. In the higher dose ranges, such as are used in radiation therapy, it seems most probable that both factors contribute to tissue death (Koller, 1947; Lasnitzki, 1947).

2. *Tissue Damage Caused by Radiation*

The reaction of tissues exposed to ionizing radiation is obviously a consequence of damage to and death of its component cells. Since the

clinical response in patients with the acute radiation syndrome is determined by tissue damage of individual organ systems, it is important to consider carefully the manner in which such damage occurs.

a. *Delayed manifestations of tissue damage in animals subjected to whole-body radiation*

If the tissue reactions in man and animals are considered in the light of the data presented above, one would expect the "delayed" or chromosomal type of cellular death to predominate as a result of the doses of total-body radiation usually responsible for the acute radiation syndrome (50 to 1,500 rem). This is borne out by clinical and histologic observations. An obvious clinical example of delayed damage of tissue is found in the case of skin heavily treated with high voltage x-rays; here, epidermolysis may not occur for a week or more after exposure. Histologic evidence of cellular destruction also is seen only after a period of delay which varies from tissue to tissue. For instance, in the case of lymphoid tissue of rabbits given 800 roentgens of x-rays, the delay in cellular death is only 30 minutes, whereas in the epidermis of mice exposed to 5,000 rep of beta rays, marked histologic damage is delayed for 10 days (Bloom, 1948).

The latent period before damage of tissue becomes manifest and the rate at which destruction proceeds deserve further consideration.

(1) *Latent period preceding tissue damage:* There is no direct experimental evidence which explains the variability in the latent period before cellular death and in the rate of destruction of tissue of different organs. However, one can postulate a mechanism which would account for such variations. Thus, it has been shown that most cells with severe chromosomal damage do not die until they attempt to divide. Death, therefore, is delayed until the tissues recover from the radiation-induced inhibition of mitotic activity. The rate at which the tissues recover their ability to proliferate is known to vary for different organ systems (Knowlton and Hempelmann, 1949). For example, in mice exposed to sublethal doses of x-rays, the lymphatic tissues and intestinal epithelium begin to proliferate soon after irradiation, whereas recovery of mitotic activity in the epidermis is delayed for a matter of days. The latent period before cellular death and also the rate of destruction of these tissues show comparable variations. Why such chronological differences in the response of different tissues exist is not clear. It has been proposed that the time of the tissue response might be correlated, in a general way, with the life span of individual cells in the tissue (Knowlton and Hempelmann, 1949). According to this hypothesis, a tissue composed of short-lived cells will respond promptly to radiation, while tissues whose cells have a long life span show a longer latent period.

Actually, the knowledge of the intermitotic time of cells in normal tissues is limited and is complicated even in simple tissues by the fact that cells are in different stages of maturation, each of different life span. Generalization of this theory to all tissues is not justified at this time. In certain tissues, however, if the values given for intermitotic times are reliable, this concept

holds true and may be used as a working hypothesis. Thus, the epithelium of the small intestine, whose intermitotic time in the rat is said to be 1.35 to 1.57 days (Leblond and Stevens, 1948), undergoes prompt and rapid destruction after irradiation. In contrast to this tissue, consider the more slowly proliferative human skin, the life span of whose basal epithelial cells has been calculated to be 129 days (Hoffman, 1949). Clinically and histologically, epidermolysis develops slowly and lasts for a number of weeks. Finally, examples of very slowly proliferating or nonproliferating tissues are provided by the liver, muscle and nerve cells. Death of cells due to chromosomal damage, if our assumptions are correct, should be rare or should not occur at all in these tissues. Histologic studies indicate that cell death is unusual in these radio-resistant tissues except with very high doses.*

(2) *Other factors influencing tissue damage:* Although it is tempting to try to simplify the concept of radiation injury by explaining all phenomena on the basis of inability of the injured cells to divide successfully, it must be stressed again that environmental changes contribute to the destruction of tissues. Delayed cellular death can well be due, in part, to the action of radiation on the blood vessels and to other changes in the cellular environment. Also, it should be pointed out again that extremely large doses of radiation can cause prompt cellular death even in nonproliferating tissues. Thus, extensive cellular destruction was noted in all types of tissue, including the muscle and brain of rabbits, at the end of a three hour period of exposure during which 50,000 roentgens of x-rays were administered (Henshaw, 1943).

b. *Variation in tissue radiosensitivity*

The wide variation in the degree of injury suffered by different organs of an animal exposed to radiation has been the subject of much discussion. In the early days of study of the biologic effects of radiation, a law was formulated to be used as a guide in predicting the response of normal and tumor tissues to radiation. The postulate, sometimes called the "Law of Bergonie and Tribondeau" (1906), or also the "Law of Lacassagne" (Muller 1950), states, in effect, that the radiosensitivity of a tissue is directly proportional to the mitotic activity and inversely proportional to the degree of differentiation of the cells. In practice, there are many exceptions to the proposed generalization.

While it is true that there are great differences in radiosensitivity, as, for instance, between a nerve cell and a lymphocyte, it is important to bear in mind that there are no absolute and clearly defined categories of radiosensitivity. It seems advisable, therefore, to follow an arbitrary classification, such as has been used in the study of the radiosensitivity of neoplasms

* Although in these few cases the facts fit the hypothesis, it is obvious that this is a great oversimplification of the true situation. For example, in the case of the liver, the high glutathione content and low oxygen tension of the tissues, rather than the low proliferative rate, may be responsible for the radio-resistance of liver tissue (L. L. Miller, personal communication). Other factors undoubtedly play a part, not only in radio-resistance but also in the time of response of tissues.

(Warren, 1941). In this scheme, tumors are placed in the following broad and ill-defined groups: (1) radiosensitive, (2) radio-responsive, and (3) radio-resistant.

If such a classification is applied to normal tissues, the blood forming organs and reproductive tissues fall into the first, or radiosensitive, group; the epithelium of the gastrointestinal tract, the skin and the connective tissues can be placed in the radio-responsive group, and the radio-resistant group is composed of the cells in the remainder of the organ systems of the body.

As mentioned previously in this section, the sensitivity to the actions of radiation is undoubtedly the result of many factors inside and outside the cell itself. One factor which would appear to influence tissue radiosensitivity is the proportion of cells in the premitotic phase during which radiation injury is readily produced. Another factor is the vascularity of the tissue. Since, however, neither of these measurable characteristics gives a satisfactory guide to radiosensitivity, it may be assumed that there are other unknown factors which are important in determining the response of cells to the damaging actions of radiation.

c. *Regeneration of radiation-injured tissue*

Regeneration of a tissue injured by ionizing radiation may occur before cessation of tissue destruction or at a variable time thereafter. The degree to which a tissue regenerates depends upon the number of surviving stem or mother cells and upon the innate ability of the surviving cells to proliferate. It also depends upon the damage sustained by the vascular supply of the tissue. For example, the atrophic nature of the skin covering an old x-ray burn undoubtedly is a reflection, in part, of the poor vascular supply. What factors govern the time at which regeneration starts are not clear. Healing of the epithelium in an acute x-ray ulcer may be delayed for months and then occur suddenly and rapidly. Waves of destruction and regeneration have been described in some tissues, and these phenomena also are beyond explanation at present.

d. *Contrast of radiation-induced tissue damage with that caused by other toxic agents*

It should be emphasized that the delay in the occurrence of death of tissue differentiates radiation injuries from those produced by other physical agents, such as heat or electricity. The latter cause immediate cellular death, presumably by coagulation of cellular proteins. The clinical picture in the acute stage of thermal burn injuries, for example, represents the sum total of the reactions of the body to localized and usually superficial dead tissues which were killed at the time of the injury. The clinical response in acute and subacute radiation injuries, on the other hand, is the local and systemic reaction to dead and dying cells which persist in selected tissues throughout the body for a matter of weeks. The prolonged period of tissue destruction is not unlike that in certain chemical poisonings or bacterial infections.

3. Systemic or Constitutional Response of the Irradiated Individual

Death or damage to tissue anywhere in the body may lead to a systemic response on the part of the body as a whole. The body reacts both to the toxic materials released by the dead and damaged tissues and to factors secondary to such damage (infection, fluid loss, etc.). The general pattern of the systemic response is the same in the case of many injuries or diseases in which breakdown of tissue is prominent, but each condition has its own unique aspects due to the type of tissues involved. In the acute radiation syndrome, the systemic response is further modified by the fact that some of the organ systems which usually participate in the response — the bone marrow, for example — are themselves injured. The factors responsible for the systemic reaction in the acute radiation syndrome are now considered.

a. *Toxic products given off by damaged tissues*

It is generally agreed that dead or injured tissues give off toxic substances which, when discharged into the general circulation, are responsible for much of the systemic or constitutional reaction of the body as a whole. The exact nature of these noxious materials has not been established, but histamine-like substances, degradation products of proteins (peptones) or nucleic acids (adenyl compounds), have been suspected of being the active factor released by damaged tissue. The toxic agents need not necessarily be breakdown products of the tissue itself but may result from the inflammatory reaction or from exotoxins produced by bacteria multiplying rapidly in the damaged tissue. Thus, pyrexin, a glycopeptide which produces fever when injected into animals, has been extracted from inflamed tissues (Menkin, 1947). Also, toxins from *Clostridium welchii* and other anaerobes have been shown to be important in the production of experimental traumatic shock in animals (Aub, 1944).

Certain experimental work suggests that much of the biologic active substances given off after injury is derived from injured rather than dead cells. Thus, yeast cells exposed to sublethal doses of ultraviolet radiation elaborate and discharge into the suspending medium much larger amounts of substances with growth-promoting properties than do untreated or killed cells (Loofbourow, 1948). Histologic studies suggest that some of the toxic substances liberated as a consequence of a thermal burn are formed by the injured cells at the margin of the dead tissue (Leach, Peters and Rossiter, 1943; Peters, 1945). There is no experimental work indicating that an analogous condition occurs in tissues injured by ionizing radiation. It seems likely, however, that under certain conditions (such as in the markedly inflamed tissues of the upper arms of cases 1 and 3), a large share of the toxic products which caused the systemic response could come from radiation-injured but still viable tissues.

b. *Disturbance in organ function produced by radiation*

Obvious disturbances of the function of organs, such as the interference with production of granulocytes by the bone marrow and the breakdown of the intestinal barrier by damage to the epithelium, need not be discussed.

The more subtle functions of tissues, such as secretory activities, also may be altered by radiation. For example, the ability of the body to form antibodies is depressed after exposure of an animal to moderately large doses of irradiation (Craddock and Lawrence, 1948). Similarly, the decreased secretion of saliva caused by irradiation of the salivary glands is well known. The effect of radiation on the activity of the adrenal gland also has been demonstrated (Patt, 1947). The resultant reaction of the adrenal glands may be responsible for some of the constitutional reactions of the irradiated animal. It may be assumed that the function of all organ systems is disturbed to some degree (depending upon the radiosensitivity of the tissue and upon the dose) by the exposure of an animal to a large or moderately large dose of penetrating ionizing radiation.

c. *Factors secondary to organ damage in radiation injury*

Many factors secondary to damage of organ systems play a prominent rôle in determining the acute reaction in the radiation-injured animal. For example, invasion of the body by intestinal bacteria unquestionably influences the terminal clinical response and may even cause the death of some animals (Bennett et al., 1949). Such invasion is secondary to loss of the intestinal epithelium, destruction of myelopoietic tissues and diminution in the ability of the body to form antibodies—all of which factors lower the resistance of the body to infection. Similarly, dehydration, unless remedied, may modify the clinical response. This is a reaction secondary to damage to the intestinal tissue. Malnutrition subsequent to loss of appetite and impaired absorption in the damaged intestines also influences the clinical picture. These and other secondary factors, some of which lend themselves to treatment, are important in shaping the systemic reaction of an individual with the acute radiation syndrome.

d. *Response of the individual to total-body irradiation*

As has been pointed out, the acute response of the individual to sublethal or lethal doses of ionization, and therefore the clinical picture as a whole, is the result of the total damage inflicted on all organ systems in the body as well as on factors secondary to such damage. It is appropriate in this connection to summarize briefly what has been said already about the effect of radiation on the organs and their component parts.

Radiation damage to each organ system is the result of two types of tissue injury: (1) the direct injury and death of cells by intracellular chemical changes or by modification of the cellular environment; and (2) the indirect injury to the tissue caused by (a) the products liberated by dead and damaged cells in the same or distant organs, and (b) the disturbed function of other interrelated organs. The extent of the damage to each organ system depends primarily upon the radiosensitivity of its cells. The rate of destruction of tissue varies from one tissue to another in such a manner that destruction and repair may go on simultaneously in different organ systems. The damage and degeneration of the tissues of various organ systems are directly responsible in themselves for many aspects of the clinical response.

In addition, factors secondary to organ damage influence the systemic reaction. Infection is undoubtedly one of the most important of the secondary factors, but disturbed fluid and electrolyte balance and malnutrition play prominent rôles in the overall response of the body. Thus, the clinical picture seen in the acute radiation syndrome is that of a generalized systemic disease, with evidence of massive breakdown of tissue in selected organ systems throughout the body, and with signs of infection and other factors consequent to such tissue damage. The symptoms due to damage of different organ systems occur at varying times in the course of the disease as a result of differences in the latent period between exposure and the occurrence of destruction of tissue in individual organs.

4. *Variation in the Response of the Individual to Total-Body Irradiation*

There is a great difference in the sensitivity of various plant and animal cells to the actions of radiation. Lethal doses for the extremes in sensitivity throughout the plant and animal world differ by a factor of 10,000 (Spear, 1946). Even in mammals, there is a great species-variation in radiosensitivity. Thus, the 30 day median lethal dose for guinea pigs exposed to 200 k.v. x-rays is 200 roentgens (Henshaw, 1944; Ellinger, 1945), whereas that of bats similarly irradiated is 15,000 to 16,000 roentgens (Smith, Svihla and Patt, 1949). There is also a variation, although less marked, in the amount of radiation required to kill members of the same species. This can be illustrated by an experiment in which groups of highly inbred mice (Carworth CF_1) of the same age and sex were subjected to various doses of hard gamma rays at a rate of 30 roentgens per minute (Henshaw, Riley and Stapleton, 1947). No death occurred in those animals receiving less than 500 roentgens. Eight per cent of the animals exposed to 500 roentgens were killed. In those mice receiving larger amounts of radiation, the percentage killed varied with the size of the dose. One hundred per cent mortality did not occur unless a dose of 1,200 roentgens or more was administered. This means that some animals survived more than twice the minimal lethal dose. The median lethal dose (MLD) which, by definition, is that dose which kills 50 per cent of the individuals within a specified time (usually 30 days after exposure) is 840 roentgens for mice of this strain irradiated with hard gamma rays at this intensity.

Variable and graded responses are also noted when limited portions of the body are irradiated. Thus the degree of the cutaneous erythema or of epilation produced by exposure to the same dose of x-rays varies from person to person. This variation in individual response, noted in localized tissue reactions as well as in the response of the body as a whole, is comparable to, although not so extreme as that observed in the toxicity or pharmacologic action of drugs and chemicals.

C. *Summary*

The basic process of ionization is described. Ionization and atomic (or molecular) excitation are the processes by which radiations impart

energy to tissue matter. The units of radiation dosage in common usage among radiologists and radiobiologists are defined in nontechnical language.

Body damage is discussed in terms of the mode of action of ionizing radiations on individual cells. Ionization affects the cell by direct perturbations of gene molecules, or direct breakage of chromosomes, or the immediate disruption of enzyme chain reactions. Indirect effects are produced on cells as a result of molecular changes initiated by ionization both inside and outside the cell.

The wide variety of reactions shown by the tissues of the human body is discussed in terms of the rate of proliferation of cells. Cells which normally show high mitotic activity are especially vulnerable to ionizing radiations. Generally speaking, cells which have sustained a lethal dose of radiation die off slowly over a period of days or weeks, lymphoid tissue and intestinal epithelial cells being important exceptions in which death occurs after a very short latent period.

The clinical manifestations of the acute radiation syndrome are the result of direct and indirect damage to all organs of the body. The syndrome is also conditioned by the mutual interactions of body organs, all of which have dead, dying and injured cells in varying proportions. The great difference in susceptibility to radiation damage which is seen within groups of tissue cells, microörganisms and mammals probably occurs in man. This will give rise to large variations in severity of the radiation syndrome. Basically, however, the symptomatology of the acute radiation syndrome simulates that of other well studied diseases which involve prominent tissue destruction, such as chemical poisoning, bacterial infection, intestinal obstruction and thermal burns.

SECTION V. CLINICAL SIGNS AND SYMPTOMS

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V. CLINICAL SIGNS AND SYMPTOMS

The outstanding feature of the clinical picture presented by these nine patients is their close conformation to the pattern of radiation injuries previously described in man and animals. The complexity of the incident radiation, the short duration of the exposures and the magnitude of the doses to limited parts of the body appear to have produced no basically new clinical phenomena. The case histories will be considered in detail, however, since these injuries are unique in certain respects. Other accounts of the acute radiation syndrome in human subjects can be found in the reports of the atomic bomb medical casualties in Japan (Medical Report of Joint

Commission), in an article dealing with a case of acute mesothorium poisoning (Hamperl and Roemheld, 1936), and with several instances of acute x-ray injury caused by teleroentgen therapy (den Hoed, Levie and Straub, 1938). Recent physiologic studies in animals exposed to total body radiation have been summarized in a report by Prosser et al. (1947-a).

To simplify discussion of the clinical signs and symptoms, this section is divided into three parts—the reaction of the hands and upper extremities, the reaction of the skin and its appendages and the systemic response. The symptomatology of the present cases is compared with that in thermally burned patients in an effort to establish a point of reference with a well known and somewhat similar type of injury.

A. *Hand Injuries*

The reaction of the hands of cases 1 and 3 was much more sudden and severe than that in other previously described radiation injuries. However, the nature and sequence of clinical events were similar, except in degree, to those in acute radiation burns of the usual type. Edema and exudative epidermolysis followed by necrosis of dermal tissues occur in this order in severe localized radiation injuries. Pain, sometimes so extreme as to require large doses of morphine, is the outstanding symptom during the acute stage of a severe x-ray or gamma ray burn (Brown, McDowell, and Fryer, 1949). Four features of the hand injuries of these cases were so remarkable as to deserve comment. They were: (1) the promptness of the appearance of edema of the hands; (2) the dry gangrene of the right hand of case 1; (3) the absence of erythema of the skin of the right hand in case 1, and (4) the marked inflammatory response of the upper arms. The treatment of the injuries (5) is also discussed.

1. *Edema of the Hands*

Swelling of both hands of case 1 was pronounced within 30 minutes after exposure, while that of case 3 appeared in a period of three hours. This tissue response was much more rapid than that usually produced by x-rays or gamma rays. Even beta radiation, which provokes prompt evidence of skin damage, has not been reported to cause visible skin reactions in man in such a short period of time (Robbins et al., 1946; Knowlton et al., 1949). The explanation for the explosive nature of the response of the tissues of the hand probably lies in the magnitude of the dose of radiation to which these tissues were subjected. Similar development of massive edema of subcutaneous tissues has been observed at the end of a three hour period of exposure in rabbits given 50,000 roentgens of x-rays (Henshaw, 1944-b). No morphologic changes were noted in the blood vessels of these animals at the end of the exposure, but marked damage and destruction of cells were observed in all other tissues, including the radio-resistant muscle and brain.

The edema which occurred in the hands of the two patients was undoubtedly the result of at least two factors—one, the increased permeability of the injured capillaries, and two, the greatly increased osmotic pressure

of the extravascular fluids created by the rapid destruction of protoplasm (Borak, 1942). The increase in osmotic pressure of these tissues must have been very great indeed to account for the ligneous character of the edema of the hand of case 3 and the tense distention of the blisters of case 1. Such a marked increase in tissue osmotic pressure and the consequent edema are compatible with the severe cellular destruction which must have occurred in all soft tissues of the hands.

The analogous edema occurring in tissues adjacent to thermal burns serves to illustrate the magnitude of the fluid shift which can result from even superficial tissue injury. Calculations indicate that for every 1 per cent of the total body surface burned, 150 c.c. of fluid (containing proteins and electrolytes) are lost from the vascular system into the interstitial spaces around the wound and through the wound surface (Cope and Moore, 1947). Although this value may be high for burns of the hand (because of the limited tissue distensibility), it shows that the flow of fluid into the interstitial spaces of severely injured tissues can be massive and may seriously affect the fluid balance of the body. In contrast to the edema of thermal burns, which reaches its maximum 36 to 48 hours after injury (Cope and Moore, 1947), the edema and loss of fluid from the wound surfaces in case 1 did not reach their peak until the second week following exposure. The continuation of fluid loss from the wound surfaces during this two week period indicates the persistence of blood flow in the damaged tissues.

2. *Dry Gangrene of Case 1*

Necrosis often develops in the dermal tissues underlying acute radiation burns of the skin (McKee and Cipollaro, 1946). The sloughing of such necrotic tissue is responsible for the formation of the typical acute radiation ulcer. As the severely damaged tissues become necrotic, they assume a white ischemic appearance resembling that seen in the exposed dermis of the dorsum of the hands of case 1. This type of tissue death is believed to be the result largely of the obliteration of small blood vessels. In case 1, dry gangrene presumably was caused by obstruction to blood flow in the larger arteries of the fingers and the palm of the hand. Clinically and histologically, this response was similar to that seen in frostbite or immersion foot. Although the gross appearance of the ischemic and gangrenous tissues differed, the pathologic processes in the vessels responsible for such changes were probably the same. In the case of the ischemic necrosis, small superficial vessels were involved, while in the gangrenous area, larger and more deeply placed vessels were damaged. In the usual superficial x-ray reaction, large vessels are not exposed to such high radiation doses as occurred in this case; hence dry gangrene of the type seen in case 1 does not occur.

3. *Absence of Erythema*

The failure of the heavily irradiated right hand of case 1 to become erythematous can be explained on the basis of the marked edema of the tissues and the tight distention of the skin. It may be presumed that these factors obscured the underlying inflammatory reaction. However, an early

disturbance in peripheral blood flow, as shown by the cyanosis of the nail beds of cases 1 and 3, must have occurred. This was probably due to the direct radiation damage of blood vessels (see C-3-a-2-c of this section), as it has been shown that elevation of the osmotic pressure in the extravascular spaces, per se, even though marked as in case 1, does not interfere with blood flow (O. Cope, personal communication).

4. *Swelling of the Upper Arms*

An intense inflammatory reaction is usually found in the tissues adjacent to the necrotic portion of an acute radiation burn of the skin (MacKee and Cipollaro, 1946). A reaction of this nature probably is the result of two factors: one, the direct injury of these tissues by radiation, and two, an indirect response of the tissues to the presence of the nearby dead tissue. It seems likely that both of these factors contributed to the swelling of the upper arms of cases 1 and 3. The rôle which such an inflammatory reaction plays in the systemic response of the individual has been pointed out (IV-B—3-).

The discussion of the response of the hands should not be concluded without emphasizing the fact that *prompt death of resting cells* undoubtedly occurred in the tissues that were exposed to the heaviest doses of radiation (Section IV-B). The cell destruction in the tissue of the hands must have been comparable in rapidity and extent to that described in rabbits given 50,000 roentgens of x-rays (Henshaw, 1944-b). This fact must be kept in mind when one compares the clinical reactions of the hands of these patients with those of other human subjects and animals that have been irradiated with smaller doses of ionizing radiation.

5. *Treatment*

The treatment of the injured hands of case 1 was patterned after that used in the therapy of thermal burns, while the treatment of case 3 represented an attempt to "amputate" by refrigeration the hopelessly damaged tissue. The use of débridement and frequently changed pressure dressings in case 1 afforded an opportunity to observe the clinical condition of the wounds. In retrospect, however, it is evident that this treatment did not control the pain or prevent the absorption of toxic breakdown products. The experience gained from the study of the hands of case 1, however, permitted a realistic evaluation of the extent of tissue injury in case 3 to be made at the time of the development of the first blister. Effective removal of the dying tissues with minimal trauma to the patient, i.e., by refrigeration, seemed to be the treatment of choice (Large and Heinbecker, 1944).

It should be emphasized at this point that prolonged refrigeration of normal skin below 15 to 18° C. causes an inflammatory type of tissue reaction Lewis, 1942), while chilling tissues below —6° C. even for a very short time causes tissue necrosis (Lake, 1917). Therefore, drastic measures such as were used in case 3 can be employed early in the course of a radiation

injury only if the hopeless degree of damage can be recognized. In the absence of good data about radiation dosage, it is possible to make an estimate of the extent of tissue injury on the basis of the clinical reaction, provided the nature of the incident radiation is known. For example, the prompt swelling and erythema of the skin caused by exposure to beta radiation are less serious prognostic signs than is a comparable early reaction due to gamma rays. Prolonged refrigeration below 18° C. of a beta ray injury which shows early swelling and blistering would therefore be contraindicated.

The use of less extreme refrigeration in the treatment of a local radiation injury has been suggested because of certain experiments reported in the literature prior to the occurrence of these accidents. Drastic temperature reduction (to about 5° C.) of newborn rats before exposure increases their ability to survive large doses of x-rays (Lacassagne, 1942). Lowering the skin temperature in human subjects prior to exposure, however, does not definitely diminish the effectiveness of roentgen-rays in producing erythema (Evans and Kerr, 1943), even though refrigeration of newborn rats raises the skin erythema dose by a factor of from 2.2 to 5.0 (Evans et al., 1941). Although refrigeration in all of these experiments had been employed *before* exposure, it was suspected that lowering the temperature (and the metabolism) of an irradiated tissue *after* exposure might also prove beneficial. Experimental evidence which has accumulated since the accidents, however, indicates that the temporary chilling of adult mice and rats and prolonged chilling of frogs have no effect on the mortality rate of the animals (Storer and Hempelmann, unpublished data; Patt and Swift, 1948-a). Refrigeration of thermal burns in man is reported to decrease edema formation and diminish infection, but it also delays healing. It is not recommended for general use in the treatment of burns except as a temporary measure to control pain, because the dangers of prolonged refrigeration are not thoroughly understood (Langohr et al., 1949).

It would seem, then, that there is little evidence to support the belief that lowering the temperature *after* exposure has a specific beneficial effect on tissue injured by radiation. Nevertheless, as has been pointed out, refrigeration of irradiated or thermally burned tissues (of limited volume) is of great assistance in controlling pain. It also diminishes bacterial growth and has the advantage of decreasing the rate at which the products of cell disintegration enter into the general circulation (Large and Heinbecker, 1944). Not too extreme chilling (above 18° C.) of the injured tissues, therefore, might help the patient survive the period of acute systemic reaction. If large volumes of tissue are chilled, it must be remembered that there is danger of seriously reducing the body temperature of the individual (Langohr et al., 1949).

6. *Summary*

In summarizing the discussion of the clinical response of the severely injured hands of cases 1 and 3, it can be said that the reactions were compatible with the prompt and extensive destruction in all soft tissue which

unquestionably was caused by the large radiation doses. The speed with which cellular death occurred differentiates these reactions from the more slowly progressing injuries caused by smaller doses of radiation. Tissue death due to impairment of blood flow appears to have been delayed for more than a week. Refrigeration of the injured tissues was helpful in controlling pain and may have diminished the constitutional reaction in case 3.

B. *Reaction of the Skin and Its Appendages*

The response of the skin of the face and abdomen in case 1 and of the skin of the abdomen in case 3 conforms much more closely in time and character to the response observed when limited areas of the body are treated therapeutically with x-rays. The appearance of erythema of the abdomen of cases 1 and 3 on the third day is not unusual for a third degree x-ray reaction. The gradual development of epidermolysis of the abdomen in case 1 over a period of three weeks suggests that death of the epidermal cells of the abdomen was delayed, in contrast to the immediate cellular death which occurred in the tissues of the hand (see Section IV B).

1. *Skin Reaction of Case 1*

Although less striking in appearance than the hand injuries, the cutaneous reaction of the torso of case 1 presents some interesting features. First of all, the severity of the reaction of the skin in the groin is in keeping with the clinical observation that the skin of different parts of the body shows varying degrees of radiosensitivity. It has been shown that the skin of the groin and axilla is the most sensitive to radiation, while the skin of the palm of the hand and sole of the foot is the least sensitive (Hermann and Pack, 1944). Secondly, the epilation of the hair of the temples and the beard, leaving the eyebrows relatively undamaged, reflects similar variation in the sensitivity of the hair follicles to the action of radiation. This has long been known to clinical radiologists. Thirdly, the perifollicular pigmentation noted around the edges of the burned area in case 1 is a type of skin reaction which is observed occasionally in a somewhat different form in patients receiving radiation therapy (MacKee and Cipollaro, 1946).

2. *Skin Reaction of Case 3*

The reaction of the skin of the abdomen of case 3 was unusual only insofar as the degree of the edema and the inflammatory reaction of the underlying tissues was concerned. This is consistent, however, with the large dose of radiation delivered to this part of the body. The gradual change in color of the torso from the intensely pigmented (sunburned) and unpigmented shades above and below the waist to the uniform deep red color which was present just before death was spectacular, but understandable.

3. *Skin Reaction of the Survivors*

The survivors showed some unusual skin reactions, one of which is the hypesthesia of the left arm of case 4. Changes in sensation are frequently observed in skin which has recovered from a third degree x-ray reaction. If

paresthesias occur as a result of x-ray therapy in irradiated skin which shows no gross evidence of damage, it is so mild in degree that it is not of clinical importance. It is conceivable that the hypesthesia in case 4 may have been related to the character of the incident radiation or the method of exposure. Thus, an unusual cellular response in this patient, similar to that seen histologically in the skin of cases 1 and 3, may have been associated with mild disturbances in sensation.

The localized epilation shown by this patient was not unexpected when one considers the type and depth dose of the incident radiation (see Section X). The transverse ridging of the nails of case 4 is a usual consequence of any injury to or nutritional disturbance of the nail bed. Its occurrence only in the more heavily irradiated left hand is consistent with the knowledge that ionizing radiation can disturb nail growth (Knowlton et al., 1949).

4. *Summary*

The discussion of the reactions of the skin and cutaneous appendages of the more heavily exposed patients may be summarized by stating that they conformed, for the most part, to the well-established pattern of acute x-ray reactions. One of the most noteworthy responses, observed only in the survivors, consists of the hypesthesia of the arm of case 4 in the absence of external evidence of cutaneous injury.

C. *Systemic Response*

The clinical response of these patients was similar to that which has been described in the Japanese injured by radiations from the atomic bomb explosions (Medical Report of Joint Commission). The symptomatology of these Japanese cases has been divided into the following four chronologic phases: Phase I, the initial reaction, consisting chiefly of prostration and gastrointestinal symptoms; Phase II, a period of relative well-being; Phase III, a gradually developing febrile period, lasting several weeks and complicated by diarrhea, ulcerations of the oropharynx, infection, hemorrhagic manifestations and epilation; and Phase IV, either death or prolonged convalescence with eventual recovery. The first phase usually lasted one day, but sometimes persisted for two or more days after exposure. The duration of the second phase was variable and in general was inversely proportional to the size of the dose. In the more severely injured patients, the toxic or febrile phase often began within 10 days of exposure, with severe diarrhea as its most obvious manifestation. In the less seriously injured group, epilation on about the twentieth day initiated the febrile phase. This was soon followed by the appearance of purpura and oropharyngeal lesions. Diarrhea was not so prevalent in this group of patients as the other symptoms. Statistical analysis of the Japanese data shows that epilation and purpura were commonly found together, and that oropharyngeal ulceration was the third most common type of lesion. Although there was evidence of marked individual variation, the severity of the response in the Japanese patients in general depended upon the size of the dose they received. As a rule, those

cases which had been fatally injured died before the end of the sixth or eighth week after exposure.

The discussion of the systemic response of the present patients will deal first with the initial reaction of the patients, then with the toxemia and last with the reactions of individual organ systems.

1. *Initial Reaction of the Patients*

The initial prostration and gastrointestinal symptoms are discussed together because they constitute the syndrome known as "radiation sickness," which is so common in patients receiving intensive x-ray therapy. The severity of the syndrome shows marked variation from one individual to another and cannot be correlated with the integral or volume dose (Ellis, 1945). This is demonstrated in the present series of cases by the fact that the initial reaction of case 1 was much more severe than that of case 3, even though his radiation dose was smaller. The reaction bears some resemblance to primary shock. There was, for example, a temporary fall in blood pressure in the more severely injured patients of this series. Transient hypotension is also observed in animals, particularly in rabbits, given larger doses of total body radiation (Prosser et al., 1947-a). Hemoconcentration has not been reported in animals. That which occurred in cases 1 and 3 was probably due to the dehydration which resulted from repeated vomiting. The cause of the initial reaction has not been established, as can be seen by referring to the 16 distinct theories of the etiology of radiation sickness listed in a recent article (Shorvon, 1949).

The improvement in the clinical condition of the patients who showed an initial systemic reaction was striking in its contrast to their illness of the first day. Although all patients were kept at bed-rest and did not exert themselves during the first few days after exposure, it was apparent that the more seriously injured patients were not well during this period. Weakness and exertional dyspnea were most notable in case 1. A similar failure to recover completely from the initial illness was also noted in the Japanese (S. Warren, personal communication). Many seriously injured Japanese are reported to have walked many miles and to have performed work of other kinds, but it is believed that they exerted themselves only because of necessity. The period of relative well-being in the injured Japanese lasted from a few days up to three or four weeks. It was observed that the longer this latent period, the better was the prognosis of the patient. In cases 1, 3 and 4, however, the period of well-being lasted less than one week, despite marked differences in the severity of their illness.

2. *Toxemia*

Toxemia, as judged by fever and tachycardia, occurred only in cases 1, 3 and 4. Comparison of the temperature and pulse charts of these patients suggests that the toxic phase of the illness began about five or six days after exposure. Cases 1 and 3 had a mild elevation of temperature dating back to the time of admission to the hospital, whereas case 4 did not have a significant early fever. On the sixth day after exposure, case 1 showed a

gradual rise in temperature and an abrupt increase in pulse rate. Cases 3 and 4 showed a distinct rise in temperature and pulse rate on the fifth and sixth days, respectively. These observations would suggest that the absence of fever during the second week after exposure to ionizing radiation may be a favorable prognostic sign. However, it is not entirely clear that this is so, as there is a good possibility that this febrile episode in case 4 does not represent the true third or toxic phase of his illness (discussed in part C-9 of this section).

Despite the more rapid progress of the illness of case 3, his fever was never so high as that of case 1. This may have been due to the fact that the chilling of the upper extremities, a substantial proportion of the total body mass, prevented the temperature from reaching its full height. That refrigeration of the extremities can influence body temperature is shown by an experiment with thermally burned dogs. In those dogs with four burned legs, all of which were chilled, the fall in body temperature was sometimes so extreme as to jeopardize the life of the animals (Langohr et al., 1949).

Data about fever in the Japanese patients are meager, particularly for the period immediately after exposure (Medical Report of Joint Commission, Section 2). Nevertheless, there is a record of elevation of temperature in a few patients during the first few days. Fever was prominent in the patients who died during the first week or so after exposure. A stepwise increase in temperature until death was reported in many of the fatally injured patients, but all types of fever curves were seen. In the less severely injured patients, fever occurred during the toxic phase of the illness several weeks after exposure. It is not clear from the Medical Report of the Joint Commission whether these patients had fever during the second phase of their illness.

The etiology of the fever and toxemia in patients and animals with the acute radiation syndrome deserves comment. Early in the disease, exogenous causes such as infection are not clearly present.* It seems likely, therefore, that the early fever in patients with radiation injury, as well as that noted in persons with severe thermal burns, represents a response on the part of the body to the products of tissue breakdown. That tissue degradation occurred promptly in the present patients is suggested by the early appearance of aminoaciduria. Later in the acute radiation syndrome, however, infection, usually with intestinal bacteria, plays an increasingly prominent rôle. Thus, the blood cultures of dogs given fatal doses of x-rays over the abdomen were not positive until the fourth day after exposure (Warren and Whipple, 1923). After the fourth day, bacteremia was usual in a series of irradiated mice (Lawrence and Tennant, 1937). A correlation between positive blood cultures and mortality was observed in irradiated dogs that lived more than two weeks after irradiation (Bennett et al., 1949; C. P.

* In animals, as has been pointed out, rapid multiplication of anaerobic bacteria in injured tissue results in the elaboration of toxins which play an important rôle in the development of experimentally produced traumatic shock (Aub, 1944). Infections of this type could have occurred in the denuded tissues of cases 1 and 3, and the resultant exotoxins would have contributed to toxemia.

Miller and C. Hammond, quoted by A. Brues, personal communication). In the fatally injured Japanese, evidence of bacteremia was often found at autopsy (Medical Report of Joint Commission, Section 2). Bacterial lesions (pneumonia, anginal ulcers in the oropharynx, and skin pustules) were frequent in the group of patients who died between the third and the sixth week after exposure (Liebow, Warren and DeCoursey, 1949). In the fatally injured patients of the present series, infectious processes in the oropharynx and possibly the pericardium of case 1, and in the pneumonic patches of case 3, undoubtedly were responsible for much of the late fever and toxemia.

3. *Gastrointestinal System*

a. *General features*

(1) *Phases of response:* The two distinct phases of gastrointestinal symptoms seen in cases 3 and 4 were also observed in the injured Japanese. The first phase occurred as a part of the initial reaction immediately after exposure, whereas the second, a more generalized reaction of the alimentary tract, became evident after an asymptomatic period of several days. In the Japanese, the second phase was often associated with diarrhea, bleeding from the bowel and necrotizing anginal ulcers in the oral cavity. Cultures of the diarrheal stools showed in only a few instances pathogenic bacteria of the dysentery type, and gross blood was present in one-sixth of the cases of one series of the Japanese patients.

The gastrointestinal reaction of case 1, unlike that in the Japanese, may be divided into three phases, even though the second and third phases were not entirely distinct. The first phase was not unusual except for its severity. The next phase, during the second week of illness, was remarkable because of the radiostomatitis which was associated with a moderate degree of paralytic ileus and an essentially nonbloody diarrhea. Radiostomatitis, although common in people receiving therapeutic x-ray treatment for cancers in the mouth, was not observed in the injured Japanese, except possibly in a few patients who died 10 to 14 days after exposure (Medical Report of Joint Commission, Section 2). It should be mentioned at this time that the dryness of the mouth experienced by case 4 two weeks after exposure undoubtedly represented a very mild form of radiostomatitis. The second phase of the reaction in case 1 showed definite improvement before it merged with the third phase, in which necrotizing ulcerations of an entirely different character developed in the buccal cavity. Although the abdominal distention was limited to the second phase, the diarrhea persisted throughout the latter part of the illness.

(2) *Reasons for phasic response:* Although the mechanism responsible for the periodicity in the gastrointestinal reactions is not clearly understood, it is interesting to consider whether the three following postulates, alone or in combination, might explain the clinical manifestations.

(a) Direct damage to different portions of the alimentary tract. The variability in the latent period between exposure and the response of differ-

ent tissues has been stressed (Section IV). It is not unreasonable to assume, therefore, that the different types of intestinal epithelium should respond at varying intervals after exposure. Indeed, the autopsy protocols of cases 1 and 3 indicate that the most intense response of the latter case, 10 days after exposure, occurred in the jejunum and ileum, whereas the only evidence of damage in the former instance (24 days postexposure) was found in the colon. Obviously a conclusion cannot be drawn from two cases, but the possibility of damage to different parts of the intestines occurring at varying time intervals after exposure cannot be excluded as a factor which might be responsible for the repetitive nature of the intestinal reaction.

(b) Indirect damage to the gastrointestinal system. Gastrointestinal reaction as an indirect manifestation of bodily damage is well known. Thus, it is possible that reflex mechanisms similar to those which cause nausea and vomiting in appendicitis, pneumonia and other severe infections may have contributed to the initial phase of the intestinal reaction. Admittedly, such a hypothesis is unnecessary to explain the initial reaction of cases 1 and 3 in view of the severe epithelial damage of the small intestine, which must have developed during the first day as a direct result of the exposure. However, in the case of patients not in the present series who experience radiation sickness after localized irradiation of parts of the body other than the abdomen, reflex mechanisms may well play a rôle in the causation of early nausea and vomiting. Another example of the rôle of indirect factors in producing damage to the gastrointestinal tract is the development of the oropharyngeal lesions already mentioned. Such injury is believed to be the result of a number of factors which lead to lowered tissue resistance to infection. Direct local tissue injury here too is an important factor, but agranulocytosis and diminished antibody production also undoubtedly play a part in the progression of these lesions. A third example of possible indirect factors which might contribute to the gastrointestinal reaction is the nonspecific intestinal manifestations which occur in many kinds of injury. For example, acute duodenal (Curling's) ulcers have been described in patients with thermal burns (Harkins, 1942). Similarly, in a series of burned patients, one-third showed guaiac-positive stools (up to 3 plus) on the fifth day after injury (Aub et al., 1943). Such reactions, which are probably related to the blood flow in the intestines after injury, may have participated in the development of the intestinal lesions in the patients under discussion.

(c) True periodicity of response in radiation-injured tissues. Since the possibility of periodicity in the gastrointestinal response has been mentioned, it is pertinent to refer to the true cyclic phenomena observed in certain tissues injured by ionizing radiations. Periodicity has been described in the reaction of the skin and buccal mucosa of human subjects, and in the liver and marrow response of animals. Thus, three distinct waves of erythema occur in the skin at different time intervals after exposure. The suggestion that cutaneous erythema depends on the rhythmical reaction of the blood vessels was first made 26 years ago (Miescher, 1925). It is now postulated

that the periodicity of cutaneous erythema is due to the action of radiation on different parts of the peripheral vascular system (Borak, 1942). The first erythema is said to be due to a capillary response; the second, to an arterial reaction; and the third, to a venous effect. It has also been claimed that tumor tissue as well as the mucosa of the oral cavity shows a cyclic response to the action of radiation, although there is not good agreement among investigators as to the interval between periods of retrogression (Coutard, 1935; Friedman and Rosh, 1939). Two waves of degeneration have been described in heavily irradiated liver tissue (Pohle and Bunting, 1932). Recently, recurring periods of cell destruction and regeneration have been observed in the bone marrow (Bloom, 1947). The cause of the cyclic tissue reactions has not been established, but it is conceivable that these waves may be related, in part, to the variations in blood flow resulting from the action of radiation on the blood vessels.

b. *Unusual features*

There are several features of the gastrointestinal response of these patients which deserve further discussion. The gastric retention of case 3, the radiostomatitis of case 1 and the changes in the gastrointestinal secretions will be considered individually.

(1) *Gastric retention:* Extreme gastric retention, presumably due to paralytic ileus during the acute stage of radiation injury, as seen in case 3, has not been reported previously, although intestinal obstruction as a late complication of irradiation of the gut is known (Martin and Rogers, 1924). It is reasonable to assume that this unusual response is the result of the intense irradiation of the abdomen of this patient.

(2) *Radiostomatitis:* Stomatitis associated with dryness of the mouth and loss of taste, such as was observed in case 1, is common in patients who have received intensive x-ray therapy for lesions in the oral cavity. However, the mucosal reaction produced by x-rays of the energy usually employed in this kind of treatment (220-kv peak voltage) is almost always accompanied by a comparable epidermal reaction. High voltage x-rays or gamma rays from radium, in contrast, produce a more severe mucosal reaction than cutaneous response (Friedman and Rosh, 1939). This is explained by the fact that strong tissue ionization occurs further below the surface of the skin in the case of the radiation of higher energy. In the present situation, where neutrons of limited range caused the major portion of the tissue damage, the mucosal reaction cannot be attributed to a high depth dose. It is also impossible to explain the reaction by assuming increased scattering of the neutrons by the teeth.

As will be shown later (Section VII), irradiation of the adjacent tissues by the neutron-induced radioactivity in the teeth and other bony structures cannot be ignored but probably did not contribute significantly to the total mucosal dose. On the other hand, the intense radiation from the highly radioactive gold inlay in case 3 caused a localized tissue reaction.

The brevity of the exposure to intense neutron radiation may explain the mucosal reaction, since it has been found that the relative intensities of the cutaneous and mucosal response to neutrons depend upon the time interval during which the tissues are irradiated (Stone and Larkin, 1942). Thus, when oral lesions were treated with high energy cyclotron neutrons (21-Mev maximal energy), the reaction in the buccal mucosa was more severe than that in the overlying skin, provided the fractionated doses were given within a period of 12 to 14 days. If treatment was protracted, however, the cutaneous effect was more extreme than the mucosal reaction.

(3) *Gastrointestinal secretions:* The presence of combined acid in the gastric secretions of case 3, on the sixth day after exposure, and the lack of mucus in the stools of all patients are noteworthy. Irradiation of the abdomen of patients and animals with large doses of x-rays is known to cause a diminution of the free and combined acid in the gastric secretions (Desjardins, 1931). The fall in gastric acids occurs before the pepsin content is decreased. In a small group of Japanese patients, the incidence of anacidity and hypoacidity was not unusual. The fact that the combined acid content of the vomitus of case 3 was normal is surprising only in view of the exceedingly large radiation dose delivered to the abdomen. The absence of increased amounts of mucus in the stools of these patients, on the other hand, is distinctly unlike the findings in irradiated animals, where fecal mucus is prominent (Prosser et al., 1947-a).

4. *Cardiovascular System*

The circulatory collapse noted in case 3 was in all probability related to the severe adrenal damage. This will be described in greater detail in Section IX, where the similarity between the pathologic findings in the adrenals of this case and in those of patients with acute infections will be stressed. The circulatory collapse also calls to mind experimental work which emphasized the resemblance between the systemic reaction to radiation injury and the circulatory collapse observed after intestinal obstruction and thermal burns (Moon, Kornblum and Morgan, 1941). The prostration, vomiting, diarrhea, early leukocytosis followed by agranulocytosis, hemoconcentration and absence of early fever are similar in dogs injured either by radiation or by ligation of the bowel. Hemoconcentration, however (a prominent early finding in case 3), does not appear in irradiated animals for several days. The severity of the systemic reaction in experimental animals is said to parallel the amount of damage to the intestinal epithelium (Moon, Kornblum and Morgan, 1941).

The arrhythmias and pericarditis of case 1 call attention to the possible action of ionizing radiation on the heart. The heart is believed to be very resistant to radiation (Desjardins, 1931). However, functional disturbances in cardiac action were observed in some of the Japanese patients (Medical Report of Joint Commission, Section 2). Thus, hemic murmurs and accentuation of the second pulmonary sound were reported, as well as disturbances in the electrocardiographic pattern (low T waves, depressed

ST segments and left axis deviation). Electrocardiographic changes in the T waves were also seen terminally in irradiated dogs which developed myocardial hemorrhages (Prosser, Painter and Swift, 1947-b). Extrasystoles, but an otherwise normal electrocardiogram, were recorded in the case of acute mesothorium poisoning (Hamperl and Roemheld, 1936). Such symptoms are, for the most part, nonspecific and of the same nature as the abnormality of the heart sounds noted in case 3. The fever and toxemia may well have been responsible for these functional changes.

On the other hand, paroxysmal auricular tachycardia and pericarditis such as were observed in case 1 have not been described in man or animals with fatal radiation injuries. Arrhythmias of this nature, however, are common in persons with Wolff-Parkinson-White syndrome, a defect in the myocardial conductive system, which case 1 was known to have (White, 1944). It seems probable that the added strain of the severe illness or the beginning of the pericardial inflammatory reaction at this time must have precipitated the disturbance in rhythm. Therefore, this episode probably does not represent a specific effect of the radiation.

The discussion of the nature and etiology of the pericarditis of case 1 will be deferred until Section IX.

5. *Jaundice*

No case of clinical jaundice was noted in the Japanese, even though one instance of elevated icteric index was reported (Medical Report of Joint Commission, Section 2). Although there is laboratory evidence of liver damage in animals seriously injured by radiation, no instances of frank hepatic failure or of gross icterus of the blood serum and tissues have been reported. In contrast to these observations in irradiated human subjects and animals, jaundice is sometimes noted in patients with severe thermal burns (Harkins, 1942).

The absence of jaundice and other signs of severe liver damage indicates that the functions of the liver cells are not seriously disturbed following exposure to lethal doses of total body radiation. Perhaps the prolonged period of tissue death throughout the body with the consequent gradual, rather than sudden, release of degraded products of protoplasm into the circulation, allows the liver cells to keep up with the required detoxification. Also, the absence of early hemolysis in the radiation-injured individual means that the body is not flooded with bile pigments soon after injury, as occurs in thermally burned patients.

The rapid development of jaundice in case 3 during the terminal hours of life is a significant observation. It was probably the result of hemolysis and hepatic failure occurring just before death. The evidence for increased hemolysis is presented in Section VI. That liver damage existed in case 3 is shown by the porphyrin excretion studies, by the decreased prothrombin level during the last two days of life, and by the histologic observations (see Section IX). The large dose of radiation delivered to the abdomen must have contributed to this severe degree of liver damage, although liver injury

secondary to tissue damage elsewhere in the body undoubtedly was an important factor. It should also be mentioned that case 1, who received a similar high abdominal exposure, also showed bile in the urine sample passed during the last day of life.

6. Genitourinary Tract

Study of the renal function in these cases was limited to urine output, urinalysis and nitrogen retention determinations. They indicate that a serious interference with renal function occurred only in case 3. These findings are similar to those noted in the Japanese, in whom few disturbances in renal function were observed (Medical Report of Joint Commission).

Detailed study of the renal physiology in irradiated dogs by direct (phenol red, creatinine and urea clearances) and indirect methods (blood non-protein nitrogen and water excretion) is indicative of an enhanced renal function during the febrile or toxic phase of the illness (Prosser, Painter and Swift, 1947). It has been suggested that this alteration may be due to increased blood flow, general increase in catabolic processes or to the increase in the plasma : cell ratio. In the terminal stages of the illness of fatally injured animals, renal failure often occurred.

The testicular damage, including the loss of organ weight and aspermia of cases 1, 3, and 4, will be discussed in Section IX.

7. Weight Loss

The loss of weight noted in the more severely injured patients is also observed in animals exposed to large doses of total body radiation. In dogs, for example, the body weight decreases when the dose exceeds one-third the median lethal dose (Prosser, Painter and Swift, 1947). The loss of weight is not rapid during the first week following exposure but is accelerated during the second and third weeks. Fatally injured animals which survive for several weeks may lose as much as 25 per cent of their preëxposure weight. The loss of weight cannot be explained on the basis of dehydration resulting from diarrhea and vomiting. As a matter of fact, studies of the fluid balance in rats are controversial. They have been said to show water retention rather than loss (France, 1946), but recently a post-irradiation diuresis has been described (Edelmann, 1949). In the past, the loss of weight resulting in "radiation cachexia" was attributed to intestinal injury, as it had been observed in dogs after irradiation of isolated loops of gut (Martin and Rogers, 1942). Recent experiments indicate that decreased food intake and enhanced catabolism are probably the most important factors in the decrease in weight (Prosser, Painter and Swift, 1947). Furthermore, the elevated basal metabolism in irradiated rats (Kirchner, Prosser and Quastler, 1949) is a factor which also presumably contributes to loss of weight.

In the present series of cases, the aminoaciduria in the more severely injured patients and the high potassium excretion in case 4 may be explained, in part, by assuming that tissue breakdown was enhanced. Patients with severe thermal burns also lose weight and go into a negative nitrogen

balance of a mild degree (Aub et al., 1943). It is hard to attribute the increased nitrogen output in burned patients to excretion of degraded tissue protein, since the potassium balance is usually unchanged. The marked elevation in the basal metabolism of thermally burned patients may also play a part in producing loss of weight (O. Cope, personal communication).

8. *Hemorrhagic Lesions*

Spontaneous hemorrhagic manifestations are such a characteristic finding in human subjects and animals fatally injured by radiation that their absence in these cases, except terminally in case 3, deserves comment. In the animals irradiated during the Bikini tests, extravasation of blood which occurred in almost every tissue of the body was the earliest and most consistent gross lesion (Tullis and Warren, 1947). Gingival bleeding followed by hemorrhages into the skin and bowel was observed in many of the injured Japanese who survived for three weeks or more after exposure (Medical Report of Joint Commission, Section 2). Similar extensive bleeding unquestionably would have occurred in case 3 had life been prolonged. Studies of the clotting time in the survivors of the second accident indicate that subclinical disturbances in the clotting mechanisms of the blood were present. It is not known whether these patients showed increased bleeding tendency or enhanced capillary fragility. The disturbances in blood clotting will be discussed further in Section VI.

It is interesting to note that some patients in whom epilation occurred (including cases 1 and 4) did not develop hemorrhagic manifestations, since, as has been pointed out, these two symptoms were frequently associated in the Japanese. The fall in platelets in case 4 at the time of epilation suggests that a subclinical disturbance in the clotting mechanism existed during the third week after exposure. The fact that gross bleeding did not occur probably can be explained on the basis of the limited tissue penetration by the neutrons. This allowed some of the deeply placed blood-forming tissues to be spared from severe damage. (See VI-B-2-c for a discussion of the hematologic response in animals with shielded spleens, p. 419.)

9. *Delayed Weakness and Fatigability*

The delayed weakness in case 4 after the period of well being was a notable symptom. Whether the development of the weakness was delayed for two weeks or whether it merely became manifest when the patient overtaxed his strength on leaving the hospital is not clear. It is difficult to believe that this patient would have misjudged his strength and endurance so completely had not the weakness become more pronounced at this time. It seems entirely possible, in retrospect, that this period of delayed weakness and fatigability corresponds to the third, or febrile, phase of the acute radiation syndrome, and that fever, if it occurred, was overlooked. In the Japanese, this stage of the illness was frequently heralded by epilation. Thus, the loss of hair and relative thrombocytopenia in case 4, occurring at the same time as the weakness and prostration, suggest that this episode actually was the third stage. If this is true, the early febrile reaction of

case 4 (during which prolongation of the blood clotting time was noted) was a complication which either did not occur generally, or was not serious enough to have been mentioned in the Japanese case reports.

Prolonged weakness was also noted in the Japanese survivors, some of whom had not recovered their sense of well being by the end of the third month after exposure (Medical Report of the Joint Commission, Section 2). This weakness does not seem to be analogous to the diminution in physical endurance observed in mice which had survived a median lethal dose of neutrons (Stapleton and Curtis, 1946). These mice, although normal in other respects, showed a progressive loss of vitality throughout their lives, whereas the patients in the present series and in Japan returned to a state of apparently normal health. While on the subject of the delayed weakness, it should be emphasized that case 6 showed neither loss of strength and weight nor epilation.

The correlation of the weakness with the disturbance in excretion of the corticoid-like material, and the salt hunger of case 4 suggest that the symptomatology may have been associated with adrenal dysfunction. More will be said about the significance of the urinary corticoid-like material and the eosinophil counts of this patient (in Sections VI and VII), and about the experimental evidence for adrenal dysfunction in acute radiation injury (Section IX).

10. *Absence of Symptoms in Cases 2 and 6 Through 10*

It is important to emphasize the absence of symptoms in cases 2, 6, 7, 8, 9 and 10. Previous observations have indicated that some patients can tolerate as much as 100 roentgens of total body radiation given therapeutically without experiencing symptoms (Cantril et al., 1947). If one considers the radiation doses of the present cases solely in terms of energy absorption (ignoring the important factor of depth dose), it can be computed that case 6 received the equivalent of 92.4 roentgens of gamma rays, and that the other asymptomatic survivors received correspondingly smaller doses. These observations, then, are in line with the previous reports of the magnitude of the radiation doses which can be tolerated without producing symptoms.

11. *Treatment*

Treatment of the systemic reaction of these patients was entirely supportive, and was directed at assisting the body to survive the acute febrile period. As in thermal burns, there is no specific therapy for fatally injured tissue. Unlike the situation in thermal burns, there is no surgical or other means of helping to repair injured tissues, except where the radiation injury is superficial and localized (Brown, McDowell and Fryer, 1949). Regeneration of an injured tissue is, therefore, completely dependent upon the number of cells which survive, their capacity for regeneration and the adequacy of the blood supply. At the time of these accidents, the only therapeutic measure believed to have a specific action directed at controlling one of the manifestations of radiation damage was the use of toluidine blue to

counteract the increased amount of anticoagulant in the blood. (See Section VI.) This was not used in the absence of clinical bleeding.

a. *Consideration of specific drug and hormone therapy*

A brief consideration of the drugs and other methods used to treat radiation sickness in patients receiving x-ray and radium therapy, as well as those tested in animals for their action in prolonging life and in the sparing of certain tissues, illustrates how limited are the specific methods of treatment. Almost every conceivable drug, including sedatives, sodium chloride, hydrochloric acid by mouth, antihistamine compounds, Dramamine, liver extract and vitamins, particularly those of the B complex, have been tested on patients receiving x-ray therapy. Each type of drug has advocates who believe in its effectiveness in preventing radiation sickness, but the true value of most of the methods, except possibly for the salt and antihistamine derivatives, is not clearly established (Painter and Brues, 1949).

Similarly, saline, vitamins, pentnucleotides, bone marrow and adrenal cortical extracts, nucleic acids, atropine, rutin and associated flavones and body refrigeration have been used in attempts to increase survival or prolong life in irradiated animals (Simmons et al., 1946; reviewed by Selle, 1949). Of these, only the administration of physiological saline and antibiotics seems to be unquestionably beneficial to the animals when given *after* exposure (Painter and Brues, 1949). Aureomycin and terramycin, which combat infections due to certain gram-negative intestinal bacteria, appear to be particularly effective in controlling the diarrhea and in prolonging the life of irradiated dogs (Bennett et al., 1949-b; Howland, personal communication, 1950). Similarly, streptomycin and other antibiotics appear to be valuable in combating the infections in radiation-injured mice (C. P. Miller, quoted by A. Brues, personal communication). Some reports, however, claim that desoxycorticosterone and rutin increase the duration of life of irradiated animals (Ellinger, 1948; Field and Rekers, 1949), but the value of these drugs is questionable (Straube et al., 1949; Cronkite et al., 1948-a). Recently, atropine given one day before irradiation and daily thereafter has been shown to reduce the radiation mortality in mice (Larkin, 1949).

There are a number of substances which, if given to animals *before* exposure, will protect against radiation effects.* Of these, cysteine produces

* The mechanisms by means of which the various procedures mentioned here and in the succeeding paragraph counteract the damaging effects of radiation are not completely understood. However, in the case of two of the procedures (pretreatment with sulfhydryl-containing compounds and reduction of the oxygen tension), there is reason to believe that protection is achieved by a modification of the activated products of irradiated water. Thus, flooding the tissues with free sulfhydryl groups provides an easily oxidizable substrate which can react with activated water products. The oxidation of such molecules, which are non-essential to cell function, spares vital enzymes and other important intracellular molecules. (See Patt, Argonne National Laboratory quarterly Progress Report, 4401, page 75, 1950, for evidence not in keeping with this concept.) The protection afforded by reduction of the oxygen tension also is probably a consequence of a modification of irradiated water. In this case there is a decrease in the number of chemically active radicals produced by irradiation, rather than a neutralization of the existing products (mentioned by Barron,

one of the most dramatic results (Patt et al., 1949-b), but glutathione (Chapman et al., 1949), as well as vitamin C, pentose nucleotides and nicotinamide (Painter and Brues, 1949), also increases the life span and survival rate if given prior to irradiation. Estrogen (estradiol benzoate) given nine days before irradiation also decreases the mortality rate, presumably because of its stimulating effect on myelopoietic tissue (Treadwell, Gardner and Lawrence, 1943; Patt et al., 1949-a). Similarly, a limited study suggests that preëxposure injections of foreign protein offer some protection to mice exposed to lethal doses of radiation (Graham and Graham, 1949).*

b. *Physiologic considerations*

A number of physiologic methods of protecting tissue against radiation damage and of treating already injured tissues have been studied. Many of these have not been successful, but four procedures have been found to be effective in helping animals survive lethal doses of radiation. These procedures are (1) shielding a portion of the blood-forming tissues from the incident radiation; (2) placing animals in a low oxygen tension before exposure; (3) drastic reduction of the body temperature in the case of newborn rats and mice, and (4) previous exposure to sublethal doses of radiation.†

Shielding the spleens of anesthetized mice raises the 30 day median lethal dose from 600 roentgens in the control animals to 1,200 roentgens in the protected animals (Jacobson et al., 1949). The splenic tissue so protected loses its lymphoid elements but promptly begins active myelopoiesis and erythrocytopoiesis. Anemia does not occur in the shielded mice, and there is rapid recovery from the leukopenia. Rendering adult rats anoxic by placing them in an atmosphere of 5 per cent oxygen for eight minutes before exposure also raises the median lethal dose by a factor of about two (Dowdy, Bennett and Chastain, 1950). This procedure is ineffective if used after exposure. As has been mentioned previously, drastic reduction of body temperature prior to irradiation has been found to enable newborn rats to survive large doses of x-rays (Lacassagne, 1944; Storer and Hempelmann, unpublished data), but temporary chilling of frogs does not produce a comparable beneficial effect (Patt and Swift, 1948-a). The prior exposure of

A.N.L., 4401, page 167, 1950). In aerated tissue, the hydrogen atoms produced by the dissociation of irradiated water react with dissolved oxygen molecules to form hydroperoxide, O.H. (See Section IV-B-1.) In the absence of oxygen this strongly oxidizing compound is not formed and, as a consequence, fewer organic molecules in the protoplasm of the irradiated cell suffer chemical modification. In those instances in which temperature reduction is beneficial to irradiated new born mice, it has been shown that the low oxygen tension in the severely hypothermic tissues plays a part in the ultimate result (Storer and Hempelmann, unpublished data).

* Recently, the following sulfur-free compounds have been found to protect bacteria to a considerable degree against the effects of x-rays: (1) glycerol, glycol, triethylene glycol and the lower alcohols (ethyl, methyl and propyl), (2) carboxylic and amino acids if utilized by the organisms but only after incubation at 37° C. for a short time and (3) certain sugars only after incubation (A. Hollaender, personal communication).

† Since this section was written, it has been shown that injections of homogenized spleen or embryonal tissues will improve the survival rate of irradiated mice even if administered *after* exposure. Transplantation of the spleen and, more recently, of the bone marrow is also said to be effective in this regard. (L. O. Jacobson, personal communication.)

mice to sublethal doses of x-rays shortly before administration of a lethal amount of radiation results in a small but statistically significant increase in survival rate (Cronkite, 1948-b).

c. *Practical considerations in the treatment of patients with the acute radiation syndrome*

The treatment used in the present patients was obviously empirical, as few of the experimental studies just reviewed had been performed before the occurrence of these accidents. However, important lessons concerning the practical problems of patient care can be learned from these cases. The signal finding which must be emphasized is that the possibility of injury should be considered for at least four weeks after exposure in persons who have received an unknown but large dose of total body radiation. The exposed individuals should be kept under medical observation until such a time as the possibility of illness is no longer present. A second lesson learned from observing these cases is the great difficulty of maintaining adequate caloric intake in severely injured persons. Food intake is diminished during the periods of gastrointestinal distress; and such food as is eaten may be poorly absorbed. Thus, experimental evidence in animals indicates a diminished absorption of fats, sugars and amino acids from the damaged gut (Martin and Rogers, 1924; Barron, Wolkowitz and Muntz, 1947; Altman et al., 1949). A third experience worthy of mention is that administration of transfusions and other intravenous medication may be difficult at times in acutely ill patients. Thus, circulatory collapse and extravasation of blood at the injection site present problems of practical importance.

Two review articles consider the best available methods of treatment of the acute radiation syndrome (Painter and Brues, 1949; Cronkite and Chapman, 1949). These articles conclude that good nursing care and hygiene, maintenance of the fluid and acid-base balance and the blood volume, replacement of blood cells and the liberal use of antibiotics are the only therapeutic measures of value at the present time. Study of the current literature (since February, 1950) and discussion with investigators working on the therapy of radiation injury in animals indicate that the basis for using most of these procedures is clinical rather than experimental. The use of antibiotics alone (J. W. Howland, personal communication) or in combination with transfusions (J. G. Allen, personal communication) has been demonstrated to be effective in prolonging life and decreasing morbidity and mortality in dogs. The value of transfusions alone has not been established in dogs (J. G. Allen, personal communication), but insufficient attention has been given to blood grouping, blood transfusion technics and other variables known to influence the clinical response in such studies. It seems clear, however, that replacement of blood cells is amply justified on clinical grounds. The use of toluidine blue is reported to have been helpful in controlling bleeding in a few persons with radiation-induced damage of the blood-clotting mechanisms (Allen et al., 1949). The toxicity of this dye in

animals has interfered with thorough testing of its potential value in total body radiation injury. The beneficial values of physical rest of the injured individual can be inferred from recent experiments which indicate that strenuous exercise increases the mortality rate of irradiated rats (Kimmeldorf, Jones and Fishler, 1950). Clinical observations made in Japan also indicate the value of rest in patients injured by radiation.

Current studies show that administration of antibiotics increases the survival rate of animals which have received radiation in doses up to the 100 per cent lethal dose and slightly above. These beneficial effects in part are related to the action of such antibiotics in combating infection or preventing invasion of the body by the usually nonpathogenic intestinal bacteria. In a certain percentage of animals, life can be prolonged to the time when spontaneous regeneration occurs in vital organs such as the bone marrow. From this evidence, it must be presumed that antibiotics will not be helpful in the treatment of injury due to doses of total body radiation much above 100 per cent lethal dose. It is also apparent that the antibiotics with a "broad spectrum" acting on intestinal bacteria will be the most effective for clinical use. Thus, oral aureomycin and terramycin have been found to be particularly valuable in treating dogs (J. W. Howland, personal communication). A problem which has arisen when antibiotics are administered over an extended period is that some of the bacteria may develop resistance to the concentrations of the antibiotic that can be achieved clinically. The simple and obvious measure of substituting terramycin for aureomycin may not prove effective, since animal experiments indicate that organisms which develop resistance to aureomycin also become resistant to terramycin, a similar antibiotic with a broad spectrum (F. Furth and J. W. Howland, personal communication).

12. *Summary*

The systemic reaction of the more severely injured patients followed the usual four phases of the acute radiation syndrome: (*a*) the initial reaction, (*b*) a period of relative well being, (*c*) toxemia associated with fever, gastrointestinal reactions, cardiovascular symptoms and bleeding, and (*d*) either death or eventual recovery. The initial reaction, most pronounced in cases 1, 3 and 4, resembled primary shock in certain respects, as it does in heavily irradiated animals. Although they felt much better during the second phase of the illness, the more severely injured patients were still moderately prostrate and weak. This failure to recover completely from the initial reaction was also noted among the Japanese but has often been misrepresented. Low-grade fever, noted shortly after exposure, occurred only in the fatally injured patients. The early fever is believed to represent a response of the body to tissue breakdown, while the high fever during the toxic phase may have been due, in part, to infection. The radiostomatitis which preceded the terminal necrotizing ulceration in the oropharynx of case 1 did not occur in the other patients (except in a very mild form in case 4) or in the Japanese. Factors which may account for the repetitious nature of the gastrointestinal reactions

are: 1) difference in the latent period preceding the response of various portions of the tract; 2) indirect or secondary intestinal reactions occurring in addition to direct injury of the gut, and 3) true periodicity apparently inherent in certain responses of tissue to radiation. The gastric retention and jaundice of case 3—reactions not described previously in the acute radiation syndrome—are probably related to the severe degree of gastrointestinal and hepatic damage caused by the extremely high dose of radiation delivered to the midsection of the body of this patient. The terminal circulatory collapse of case 3 and the striking delayed weakness of one of the survivors may represent varying degrees of the constitutional response to adrenal cortical damage. The pronounced loss of weight in the severely injured patients is a consequence of diminished food intake and possibly enhanced catabolism. The absence of hemorrhagic phenomena in the more heavily exposed patients (except case 3) is believed to be due, in part, to the sparing of the deeply placed marrow from severe damage consequent to the dissipation of most of the radiation energy in the superficial tissues of the body.

Except for the delay in the time of response and for the reactions due to damage to selected tissues (hemorrhage, lymphopenia, etc.), the constitutional reaction of these patients is similar in many respects to the illness of persons with severe thermal burns. Therapeutic measures in the acute radiation syndrome are limited to treatment of reactions secondary to tissue destruction. These include the liberal use of antibiotics, replacement of blood elements and maintenance of fluid and electrolyte balance. Certain pharmacologic and physiologic means, which minimize radiation damage if applied before exposure, are ineffective once tissue damage has occurred.

D. *Addendum: Changes in the Eyes of Case 4*

The development of cataracts in the eyes of case 4 several years after exposure may be considered to be a delayed manifestation of the acute radiation syndrome. The opacity is similar in nature to those which have been described in the lenses of persons exposed to ionizing radiations of various types. Such lesions usually take the form of an initial subcapsular haze at the posterior pole of the lens. This gradually develops into opacities which are frequently disc-shaped and clearly demarcated from the rest of the cortex. The latent period between acute exposure of the eye to x-rays and the development of the opacities is usually between six and 24 months, but may be as long as eight to 12 years (Cogan, 1950). The latent period between exposure and diminution of vision in the case of the Japanese with radiation cataracts was less than one year in one instance, and from two and one-quarter to two and one-half years in five others (Cogan, Martin and Kimura, 1949). The cataracts in cyclotron workers, which are presumably due to chronic neutron irradiation, were detected about three years after exposure began (Abelson and Kruger, 1949). Radiation cataracts may be stationary but are usually progressive. They lend themselves to satisfactory surgical removal.

The minimal acute radiation dose which will cause a cataract when delivered locally to the eye has not been established with certainty, but is of the same order of magnitude as the erythema and epilation dose (Hunt, 1947). Thus, 875 roentgens of 130-kv x-rays and 1,000 roentgens of gamma rays are reported to have caused cataracts. In the 10 Japanese with visible changes in the lens, all received an epilation dose of radiation as shown by loss of hair one to four weeks after exposure. In contrast to acute exposures, chronic or repetitive irradiation is believed to be more effective in producing permanent ocular changes than in causing a visible skin reaction (Cogan, 1950). Chronic exposure to neutrons has been shown to be highly cataractogenic in mice (Evans, T. C., 1948) and is believed to be equally effective in man (Abelson and Kruger, 1948). The R.B.E. of neutrons, as compared to gamma rays, administered in this manner in man, has been estimated to be 10 to 40.

The pathogenesis of radiation-induced cataracts is not understood. It is conceivable that the extremely slow rate of growth of the lens epithelium and, therefore, the long life span of these cells may have something to do with the prolongation of the latent periods between exposure and damage. (See Section IV-B-2-a.) Just why the damage should be more extreme in the posterior pole is not clear, since the fibers making up the bulk of the cortex are derived from the epithelium and extend from the equator to both the anterior and posterior poles.

Section VI. Hematology

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VI. Hematology

It is important to consider carefully the hematologic changes in these patients, since this response is one that is readily produced by ionizing radiation. The reader is referred to the reviews by Jacobson, Marks and Lorenz (1949), Lawrence, Dowdy and Valentine (1948), Dunlap (Warren, 1942), and Goodfellow (1936) for detailed references to observations on changes in the blood of irradiated human beings and animals.

In the subsequent discussion, the response of the blood in the present series of patients is frequently compared with that in other irradiated persons or animals. In interpreting the significance of such comparisons, two facts must be kept in mind. The first is that the conditions of exposure in the present patients were unique. Because the radiation was intense and not very penetrating, the exposures resulted in the prompt destruction of the superficial soft tissues (as in the hands of cases 1 and 3), while the deeply placed bone marrow was partially spared. Such tissue reactions did not occur in the injured Japanese and are not found in most experimentally irradiated animals. These unusual tissue reactions may explain some of the discrepancies between their hematologic response and those reported in the literature. A second fact to be remembered when the hematologic changes of these patients are compared with those in experimental animals is the variation between species in radiation reactions in general referred to in Section IV. Laboratory animals have been classified in the following manner, according to the increasing radiosensitivity of their blood and blood-forming tissues to total body irradiation with x-rays: rabbits, rats, mice, chicks, goats, guinea pigs and dogs. The radiosensitivity of man's blood-forming tissues approximates that of guinea pigs and dogs (Jacobson, Marks and Lorenz, 1949). Much of the variation between species is probably due to a difference in the sensitivity of the granulocytes, as the initial reaction of the lymphocytes appears by comparison to be less dependent upon the species (A. M. Brues, personal communication).

A. *Methods*

All pipettes and hemocytometer chambers used in this study were certified by the National Bureau of Standards. The total erythrocyte count was determined by counting two sides of a chamber filled with blood diluted and mixed in a single pipette. Four chambers of diluted blood from two pipettes were examined to obtain the total leukocyte count. The hemoglobin content of the blood was determined by the oxyhemoglobin method of Evelyn (Evelyn and Malloy, 1948). The method of Dameshek (1932) was used to estimate the number of platelets and reticulocytes. Supravital preparations and dried films of blood stained with Wright's stain were examined for cytologic changes. The usual supravital staining technic was modified by increasing the strength of the dyes (Dickie and Hempelmann, 1947). The

differential counts prior to the accident were obtained by examination of 200 fixed cells and 100 leukocytes in supravital preparations. Two hundred leukocytes in supravital preparation were counted in order to determine the postexposure hemograms. The number of refractive cytoplasmic bodies staining with neutral red in 50 lymphocytes was determined in each examination. All blood samples prior to the accident were taken between 8:30 and 10 o'clock in the morning. The first blood samples after exposure were obtained within two hours of the accidents in all cases. Subsequent samples were taken twice daily (9 to 10 o'clock in the morning and 7 to 8 o'clock in the evening) for the first few days after the accident, and then once daily except for case 1, on whom two blood counts per day were made throughout the entire illness.

The specimens of bone marrow were obtained by aspirating tissue from the sternal cavity through a 15-gauge needle. Supravital preparations and Wright-stained films of the clumps of aspirated marrow were studied for cytologic changes. The differential counts, however, were based only on examination of the supravital preparations.

The clotting time of whole blood was determined by the method of Lee and White (1913). This technic was repeated in samples of whole blood to which small quantities of an aqueous solution of toluidine blue were added in order to determine the amount of heparin-like anticoagulant in the circulating blood (Allen et al., 1948). The prothrombin time was determined by the one-stage Quick procedure (Allen, Julian and Dragstedt, 1940).

B. *Changes in the Blood Count*

Graphs showing the changes in the formed elements of the blood during the period immediately after exposure accompany each case report in Section III. However, only a limited amount of information can be gained from the study of these graphs because of their size and the way in which they are plotted. Therefore, in order to present the hematologic data in more detail, a statistical analysis of the changes in leukocyte and erythrocyte counts is provided in Appendix II. Also, the individual lymphocyte and neutrophil counts for the first two week period after exposure are listed in Appendix III. The blood counts of cases 1 and 3 were not analyzed statistically, since the changes were obvious. Because the blood count may fluctuate considerably under normal conditions in the same individual, the difficulty in interpreting changes, even after the use of statistical analysis, is obvious. The interpretation of the hematologic response is complicated further by the fact that no counts prior to exposure were available for two of the patients. Nevertheless, an attempt is made to evaluate the changes by applying statistical methods to groups of blood counts for a single individual over arbitrary intervals of time. The time intervals used in the analysis of the rapidly changing leukocyte count were shorter than those used for the more slowly changing erythrocyte count. The deviations of these averaged counts from the mean prior to exposure (when known) and from the range of normal

values (Wintrobe, 1943) were studied. Wherever possible, the trend or pattern of the deviation was determined.

1. *Lymphocyte Response*

a. *Development of lymphopenia*

Examination of the statistical data on the lymphocyte counts in Appendix II shows that lymphopenia occurred in all patients except cases 2 and 10. The most severe degree of lymphopenia in cases 4 and 6 occurred between the third and the tenth to fifteenth days. The minimal averaged lymphocyte count occurred in case 7 during the 30 to 70 day period.

The prompt and sustained reduction in the number of circulating lymphocytes noted in most of the present series of patients is understandable, since lymphoid tissue has long been known to be one of the most radiosensitive in the body. It has been shown experimentally in man and animals that a fall in the lymphocyte count occurs after acute exposure of the individual to relatively small doses of total body radiation. For example, 25 roentgens of x-rays caused a transient lymphopenia in rabbits (Jacobson and Marks, 1947), while total body irradiation of human subjects with divided doses of x-rays produced a fall in lymphocytes when the accumulated dose reached 40 roentgens (Low-Beer and Stone, 1948). The speed with which the fall in the blood lymphocytes occurs (15 to 30 minutes in animals) has been attributed to the short life time of the adult cells in the circulating blood (12 hours or less), the limited reserves of this type of cell and the immediate destruction of the parent cells in the lymphoid tissue (30 minutes) (Lawrence, Dowdy and Valentine, 1948).

Although it is generally true that more pronounced lymphopenia occurs after higher doses, the ultimate level to which the lymphocytes fall is not always proportional to the dose of radiation. However, a close correlation has been shown to exist between the early rate of fall of the lymphocyte count and the integral dose of radiation. This was demonstrated for the first time in 1936 (Goodfellow). The relationship is best shown when the blood counts of groups of people are studied collectively, for it often cannot be observed in a single individual (Ellis, 1942). If the lymphocyte count is plotted against the integral dose delivered by radium implants, the number of cells diminishes rapidly as the dose of radiation increases. This is followed by a slower rate of fall in the higher dose ranges (Bush, 1943; Price, 1948). Thus, the administration of 20 megagram roentgens of gamma radiation to the pelvis in a series of women caused a fall in the mean lymphocyte count from 2,400 to 550 cells per mm.,[8] or a decrease of 1,850 cells per mm.[8] An additional 20 megagram roentgens (total, 40 megagram roentgens) caused only a fall to 200 cells, or a decrease of 350 cells per mm.[8] Each additional increment of the same magnitude produced less of a drop in the absolute lymphocyte count.

b. *Recovery of the lymphocyte count*

It can be concluded from the study of the survivors of the present accidents that the return to the normal lymphocyte level after irradiation may

be an extremely slow process. The lymphocyte count of cases 4 and 6 was still depressed below the preëxposure level during the second year after exposure.

A similar slow recovery of the lymphocyte count was noted in patients given 60 to 120 roentgens of total body radiation for therapeutic reasons (Cantril et al., 1947). In some of these cases the lymphocyte count did not return to the preëxposure level during a 150 day period of observation after exposure. The lymphocyte count in many of the Japanese patients also was depressed at the conclusion of the study three months after exposure (Medical Report of Joint Commission, Section 6). In contrast to these observations in man, recovery of the lymphocyte count in animals is more rapid. For example, in rabbits, the lymphocyte count returns to levels present before exposure within 60 days, even after exposure to 300 roentgens of x-rays (Jacobson and Marks, 1947). It is interesting that, in both animals and man, the regeneration of parent lymphoid tissue is more rapid than is the return of the lymphocyte count. This lack of correlation between the rate of recovery of the blood and tissue lymphocytes is discussed further in Section IX.

c. *Cause of radiation lymphopenia*

Lymphopenia is found in a number of conditions unrelated to radiation injury. Thus, severe infection, advanced Hodgkin's disease or tuberculosis, chronic leukemias other than the lymphatic type, subleukemic lymphatic leukemia, and advanced agranulocytosis regardless of the cause show varying degrees of reduction of the lymphocyte count (Sturgis, 1948). However, no significant change in the circulating lymphocytes occurs in persons with thermal burns, even though generalized involution of the lymphoid tissue has been described in this as well as in other types of injury (Pack, 1926).

The lymphopenia following irradiation has long been assumed to be the result of the direct destructive action of radiation on the parent lymphoid tissue. Indirect factors originating outside the lymphoid tissue and transmitted through the blood stream have been searched for but not clearly demonstrated (Lawrence, Valentine and Dowdy, 1948; Barnes and Furth, 1943). Recently, the possibility has been suggested that an indirect effect of radiation on lymphoid tissue is mediated through the adrenal and pituitary glands (Dougherty and White, 1946).* The postulation, which is of particular interest because of the adrenal response to radiation injury discussed in Sections V, VII and IX, is based on two experimental findings. The first is that, although large doses of x-rays (200 roentgens) cause the same degree of lymphopenia and involution of the lymphoid tissue in normal and in adrenalectomized mice, small doses (10 roentgens) have an effect on the lymphatic elements only in those animals with intact adrenal glands. The

* For many years the adrenal gland has been suspected of influencing the circulating lymphocytes and the lymphoid tissue, since an increase in these cells has been observed in Addison's disease and in adrenalectomized cats (Drinker, Kent and Yoffey, 1941). Attempts to increase lymphocyte production and to raise the lymphocyte count in animals by adrenalectomy, however, are not always successful (Valentine, Craddock and Lawrence, 1948).

second observation is that lymphopenia and involution of lymphoid tissue can be demonstrated in mice, rats, rabbits and dogs following the administration of adrenocorticotropic hormone and adrenal cortical extracts (Dougherty and White, 1944; Reinhardt, Aron and Li, 1944; Farr et al., 1948). It is not clear, however, that this happens in all animal species (Valentine, Craddock and Lawrence, 1948). In man, a single dose of pituitary adrenocorticotropic hormone causes a fall in blood lymphocytes and eosinophils and a marked rise in the number of circulating neutrophils (Hills, Forsham and Finch, 1948). Protracted administration of adrenocorticotropic hormone over a four day period causes an initial drop in lymphocytes, followed by a rise which, during the course of the treatment, exceeds the level observed before treatment.

It may be concluded from this short review that the rôle of the adrenal and pituitary glands in the production of radiation lymphopenia is not clearly understood, but hormonal imbalance due to dysfunction of these glands may contribute to this response.

2. *Total Leukocyte and Neutrophil Count*

a. *Response of the patients*

The variation in the total leukocyte count from day-to-day was due largely to changes in the number of neutrophils, since the other leukocytes in the circulating blood usually remained at a relatively constant level after the first few days following exposure. The following statements, therefore, with few exceptions, can be applied to both the neutrophil response and the total leukocyte count.

All cases showed an initial leukocytosis due to an increase in the number of mature cells of the neutrophilic polymorphonuclear series. Except in cases 1 and 3, both of whom showed leukocytosis for several days, the early increase in neutrophils was not sustained but soon gave way to a condition of marked instability of the leukocyte count, which showed wide fluctuations ranging from the normal value to two or three times normal. Only case 9 showed a single count below the lower limit of normal during the first four days after exposure. With certain exceptions (notably, case 10), the height of the initial leukocyte count was roughly proportional to the dose of radiation. No constant correlation could be found in the times at which the peaks and troughs occurred in the curves of the leukocyte response for the different cases.

The initial period of normal-to-high neutrophil counts which lasted four to five days was succeeded by a neutropenia in cases 1, 3 and 4. It is significant that young neutrophils were not conspicuous until the leukopenic phase was established. The transient rise in neutrophils which occurred in cases 1 and 4 between the ninth and fifteenth days is also noteworthy. During this period there was no increase in the other cellular constituents of the blood, except for the platelets. In case 4, the only surviving patient with a clear cut neutropenia after exposure, the time required for recovery to the level of the neutrophil count prior to exposure was about two months.

b. *Initial increase in neutrophils*

Initial leukocytosis following exposure to lethal or sublethal doses of ionizing radiation has been observed before in man and animals. The leukocyte count of a patient with acute mesothorium poisoning remained at a level of about 20,000 cells per mm.^{3} for the first two days of the illness (Hamperl and Roemheld, 1936). However, such an early leukocytosis does not invariably occur in irradiated human beings. Thus, no increase in neutrophils was observed in a series of patients given a single total body exposure of from 60 to 120 roentgens of x-rays (Cantril et al., 1947). Divided doses, up to 500 roentgens, similarly did not cause leukocytosis in another group of patients (Low-Beer and Stone, 1948). Furthermore, two instances of leukopenia rather than leukocytosis were recorded in the few blood counts that were made on the Japanese during the first 24 hours after the atomic explosions (Medical Report of Joint Commission, Section 6).

In most animal species (dogs being a notable exception) leukocytosis occurs immediately after irradiation, but it is less marked and of shorter duration than that noted in these patients. Two peaks occur in the neutrophil response of rabbits, one at 12 and the other at 24 hours after exposure to either 500 or 800 roentgens of total body x-rays (Jacobson and Marks, 1947). Rabbits show an "abortive" increase, not only in the number of granulocytes but also in the number of lymphocytes and reticulocytes between the fourth and the eleventh days (Jacobson and Marks, 1947).

The initial and the abortive granulocytosis are now interpreted as a secondary reaction to tissue injury rather than as the result of the alleged stimulating effect on the bone marrow mentioned in the early literature (Bloom and Jacobson, 1948). Similar and equally prompt granulocytosis is observed in patients suffering from many other related and unrelated diseases. For example, a total white cell count of over 20,000 cells per mm.,^{3} largely due to an increase in the granulocytes, is not unusual in patients with severe thermal burns within three hours after injury (Medical Research Council, 1944). The number of granulocytes in such patients falls to normal or subnormal within two days. A second granulocytosis may occur at the end of the first week, presumably as a response to infection of the burned surfaces. Early granulocytosis is also noted in patients with circulatory collapse due to intestinal obstruction (Moon, Kornblum and Morgan, 1941).

In interpreting the early granulocytosis in the present cases, one must remember that the patients were apprehensive during the period immediately following the accidents. Therefore, emotional factors may also have influenced the initial response of the formed elements of the blood.

c. *Neutropenia*

The neutropenia that occurs in patients severely injured by radiation is well known. It is a matter of considerable interest, therefore, that none of the patients exhibited clear-cut neutropenia except for the most heavily ex-

posed, i.e., cases 1, 3 and 4. In case 4, the neutropenia was most severe during the twentieth to fortieth day of the period following exposure. The neutrophil count returned to the preëxposure level during the fifty-fifth to seventieth day interval. The neutrophil count of case 6 did not return to the prior level after the initial elevation, but that in cases 7, 8 and 9 fell to low normal (3,000 to 4,000 cells per mm.[3]). Only two of these three patients had blood counts before exposure, and, in each instance, the neutrophil count after the initial rise did not fall significantly below the mean prior to exposure.

The early blood counts made on the injured Japanese are so few that they contribute little information about the initial blood cell response to irradiation. Considerable data are available, however, regarding the degree and duration of the leukopenia (Medical Report of the Joint Commission, Section 6). The lowest leukocyte count of the fatally injured patients was almost always less than 500 cells per mm.,[3] whereas that of the survivors was usually above this level. Leukopenia in the Japanese survivors was most extreme between the third and fourth weeks. The neutrophil count began to rise shortly after this time and was usually normal by the end of the eighth week. Thus, the time of the response of the neutrophils noted in case 4 conforms well with that observed in the Japanese patients.

In interpreting the neutrophil response, as well as that of the other formed elements of the blood, one should keep in mind animal experiments, in which the conditions of exposure resemble those of the present patients. These experiments show that shielding of the spleens of mice during irradiation modified the subsequent response of the formed elements of the blood (Jacobson et al., 1949-b). In animals so protected, the degree of neutropenia was not influenced, but recovery of the neutrophil count occurred more promptly than in unprotected animals. The limited range in tissue of the incident neutrons that caused body damage in the patients under consideration means that some of the deep-seated hematopoietic tissues must have received a relatively small dose of radiation. Therefore, these conditions of exposure were somewhat similar to those in the animal experiments just mentioned, and one might expect the hematologic response of these patients to be slightly different from that seen in persons uniformly exposed to penetrating radiation. In considering the precipitous drop in the neutrophil counts of cases 1 and 3, one should also recall a suggestion for correlating the time of the fall in neutrophil count with the life span of these cells in the circulating blood (Lawrence, Dowdy and Valentine, 1948). In irradiated cats, 18 hours elapse between the time at which the neutrophil count begins to fall and the time at which the lowest granulocyte count is reached. This time is believed to be equal to the life span of neutrophils in the circulating blood. It is postulated that the good reserve of this type of cell in the body is responsible for the delay of a day or so in the appearance of neutropenia.

In considering the neutropenia that occurred late in the illness of the fatally injured patients, it should be emphasized again that agranulocytosis

may occur terminally in patients with other unrelated illnesses (thermal burns, intestinal obstruction, etc.).

3. *Eosinophil Count*

Study of the statistical data shows that there was a fall in the eosinophil count of the most heavily exposed patients. In case 4, the period of lowest eosinophil count (50 to 100 cells per mm.^{3}) occurred between the twentieth and the seventieth days. Of the six other patients, cases 6 and 8 showed a definite eosinophilia, cases 2, 7 and 9 had eosinophil counts over 250 cells per mm.,^{3} while the eosinophil count of case 10 showed no change from the preëxposure level. The eosinophilia in case 6 was striking, ranging between 550 and 750 cells per mm.^{3} in the period between two and 12.5 months after exposure. It is impossible to say that the eosinophil counts over the upper limit of normal (250 cells per mm.^{3}) in cases 2, 7 and 9 represented a true increase in eosinophils, since in two of these cases there were no counts prior to exposure and, in the third, the average count before exposure was in the high normal range (200 to 300 cells per mm.^{3}).

Eosinophilia has been said to be an inconstant finding in persons chronically exposed to ionizing radiation (Goodfellow, 1936). Many Japanese subjects showed a relative increase in the percentage of eosinophils (more than 10 per cent of the total leukocyte count), particularly in the period from eight to 12 weeks after exposure (Medical Report of Joint Commission). The percentage of eosinophils was roughly proportional to the radiation dose in the survivors. The relative increase in eosinophils was more striking in the patients at Nagasaki than in those at Hiroshima. In contrast to these observations, eosinophilia was not observed in recent human or animal studies of radiation effects (Jacobson and Marks, 1947; Cantril et al., 1947; Low-Beer and Stone, 1948).

It is interesting and perhaps significant that a fall in eosinophil count occurred only in the patients with overt signs of injury. The eosinophil count of those patients who experienced no illness either remained unchanged or was increased. It is also apparent that the depression of eosinophils in case 4 corresponded rather well in time to the period of delayed weakness. The eosinophil count, like the lymphocyte count, is influenced by the adrenal cortical hormones. Although it is probably unnecessary to explain the eosinophil response on the basis of any mechanism other than direct damage to the parent cells in the bone marrow, it is tempting to try to relate the changes in eosinophil count to the reaction of the adrenal glands. Whereas stimulation of the adrenal cortex or administration of adrenal cortical hormones produces a fall in eosinophil count, insufficiency of adrenal cortical hormone may be associated with a normal or an elevated eosinophil count (Thorn and Forsham, 1950). It is conceivable that adrenal dysfunction in these patients, suspected on the basis of other observations, may have influenced their eosinophil response.

4. *Monocyte Count*

It can be seen from the curves of the monocyte response in cases 1 and 3 that the former did not show a striking change in the monocyte count even in the terminal stage of his illness, whereas the latter showed a definite monocytopenia before death. Consideration of the statistical data on the blood counts of the survivors indicates that the monocyte count of case 4 fluctuated markedly after exposure but showed no sustained deviation from the mean count before exposure. The monocyte level in cases 6 and 10, on the other hand, showed a significant sustained increase over the average prior to exposure, while in case 9 the monocyte count increased temporarily after exposure. In case 6, the maximal degree of monocytosis (900 to 1,100 cells per $mm.^3$) occurred between the third and thirtieth days. There also appears to be a probable elevation in the monocyte counts of cases 7 and 8. In case 7, who had no count before exposure, the mean of the monocyte counts showed a steady downward trend from an initial high level after exposure of 980 cells per $mm.^3$ The averaged monocyte counts in case 8 fluctuated, but four of the six groups of counts were more than one standard deviation of the mean above the level before exposure. In contrast to these patients who showed a significant change after exposure, the monocyte count of case 2 remained constantly above the upper limit of normal, but in the absence of prior counts, one cannot say that this represents an increase.

In all of the survivors except case 4, the averaged monocyte count during the first three days after exposure was high, with extremes of 650 and 1,100 cells per $mm.^3$ The apparent increase in monocytes shown by many of these survivors is interesting in view of the delayed monocytosis described in a series of patients with rheumatoid arthritis treated by total body irradiation (Low-Beer and Stone, 1948).

5. *Basophil Count*

It is impossible to draw definite conclusions about the basophil counts in the more severely injured patients, because these cells may have been confused with toxic neutrophils. This is particularly unfortunate in case 3 because of the large number of tissue mast cells found at autopsy. (See Section IX.) In the other patients, the basophil counts are also difficult to evaluate on a statistical basis because of the normally low incidence of this type of cell. However, basophils did not disappear from the peripheral blood in cases 4 and 6, although they may have been diminished in number. The question has been raised as to whether many of the cells referred to as "toxic" granulocytes were not actually abnormal basophils, since many precursors of this type of cell have been seen in the marrow of patients subjected to total body radiation (L. O. Jacobson, personal communication). The fact that the toxic granules of the neutrophils of case 1 did not give the metachromatic color reaction with toluidine blue does not support such a hypothesis.

6. *Erythrocyte Response*

A gradual fall in the erythrocyte level associated with a comparable drop in hemoglobin occurred in case 1 during the second week after exposure and

thereafter. Case 3 did not become anemic, perhaps because of the many transfusions. Case 4 showed a decrease in red blood cells of probable statistical significance, most pronounced 40 to 70 days after exposure and lasting six to eight months (Appendix II). A lesser decrease of questionable significance in the red blood cell count of case 6 also was noted during the same 40 to 70 day interval following exposure. The drop in hemoglobin level in these cases was less than the decrease in red blood cells. The studies of the cell volume and cell hemoglobin content in cases 4 and 6 during the third week after exposures are of limited value and are not indicative of a true deviation from normal. In cases 7 and 8, the only other patients whose erythrocyte counts were analyzed statistically, there appeared to be no significant change after exposure.

A transient increase in erythrocyte level occurred in cases 1, 3 and 6 shortly after exposure. In cases 1 and 3 this may be explained on the basis of dehydration, but its cause in case 6 is obscure.

Anemia of the macrocytic and hyperchromic type is the classic finding in persons repeatedly exposed to ionizing radiation from an external source and in patients in whose bodies radioactive materials have been deposited (Warren, Dunlap, 1942). The anemia that occurs in animals after acute exposure to x-rays is normochromic (Jacobson and Marks, 1947). Patients exposed to 150 or more roentgens in divided doses showed a macrocytic anemia which reached a maximum 200 days after treatment (Low-Beer and Stone, 1948). The possible change in the erythrocyte count of cases 4 and 6, as pointed out previously, occurred much more promptly. The relatively early decrease in red blood cells noted in these cases is in accord with the observations in the Japanese survivors, in whom the lowest erythrocyte counts occurred between the sixth and seventh weeks (Medical Report of Joint Commission, Section 6). The anemias of the Japanese patients were of the macrocytic and hyperchromic type. It must be remembered, however, that the anemia in the Japanese (in some of whom the red blood count fell to 1,000,000 cells per $mm.^3$) was due, in part, to infection, thermal burns, malnutrition and other factors unrelated to ionizing radiation.

Normochromic macrocytic anemia, sometimes of a severe degree, frequently occurs in patients with other injuries, such as severe thermal burns (Medical Research Council, 1944). The anemia of burned patients is believed to be hemolytic in nature, due to the prompt destruction of excessively fragile injured erythrocytes. Experimental work suggests that this type of hemolysis results from structural changes in red blood cells that have been damaged by being subjected to a rise in temperature at the time of the injury (Shen and Ham, 1943).

Indirect evidence in animals indicates that there may also be a hemolytic factor in the production of the anemia induced by radiation (Schwartz et al., 1946). This has been proposed on theoretic grounds in order to account for the rapid development of terminal anemia in fatally injured animals. In the absence of gross bleeding, the fall in red blood cell count of these

animals is too rapid to be explained solely on the basis of the inhibition of erythropoiesis. Studies of urobilinogen excretion support but do not prove the hypothesis that hemolysis occurs. Since the fragility of erythrocytes of irradiated dogs is not increased (Prosser, Painter and Swift, 1947-b), the mechanism underlying development of possible hemolysis in the acute radiation syndrome is not clear. It has been suggested that this may be related to bacterial toxins or other factors associated with infection (J. W. Howland, personal communication).

7. Reticulocyte Count

The reticulocyte count of case 1 showed no change even in the terminal stage of the illness, whereas that of case 3 showed a gradual fall. Case 4 exhibited an increase in reticulocyte count during the latter part of the first month after exposure. The failure of the reticulocyte count to fall in case 1 is unexpected in view of the consistent decrease noted in irradiated animals (Jacobson and Marks, 1947; Lawrence, Dowdy and Valentine, 1948). It may be explained, however, on the basis of the protection from damage of some of the marrow, as has been emphasized previously.

8. *Platelets*

A fall in platelets in the peripheral blood was observed in cases 1, 3, 4, and probably in case 6. Except for case 3, whose thrombocytopenia developed abruptly on the sixth day after exposure, the decrease in platelets did not occur until the third week after exposure. The platelet count of the survivors did not reach the level usually associated with spontaneous bleeding. (See Part D of this section for a discussion of the postirradiation hemorrhagic phenomena.)

The thrombocytopenia that occurs in man and animals exposed to large doses of ionizing radiation is well known. Thus, extremely low platelet counts were observed in the severely injured Japanese within a week after exposure (Medical Report of the Joint Commission). Except for one case, significant changes in platelet count were not observed in the two series of patients treated with whole body radiation (Cantril et al., 1947; Low-Beer and Stone, 1948), but this is understandable since the doses in these cases were small compared to those received by the Japanese who showed severe hematologic changes. In animals, thrombocytopenia is reported to develop about four or five days after exposure to sublethal doses of x-rays (Lawrence, Valentine and Dowdy, 1948). These experiments have indicated that the radiosensitivity of platelets or platelet precursors is less than that of the reticulocytes. Other studies in animals have shown that the quantitative response of the platelets approximates that of cells of the granulocytic series (Jacobson, Marks and Lorenz, 1949). In view of these observations, it is surprising to find a thrombocytopenia of probable significance in case 6, who did not show a fall in either reticulocyte or granulocyte count.

9. *Summary*

All patients showed an increase in the total leukocyte and neutrophil counts immediately after exposure. In the two fatally injured patients,

both of whom had prompt and extensive destruction of the hand and other tissues, the marked neutrophilia was sustained for several days. All other patients showed a fluctuation of the neutrophil count from normal to moderately high levels during the first few days after exposure. The initial neutrophilia was succeeded by neutropenia in cases 1, 3 and 4. Lymphopenia of statistical significance occurred in all but three of the patients. In two of the survivors, the lymphocyte count did not return to the preëxposure level until the second year after exposure. A fall in eosinophil count occurred in the most heavily irradiated patients, whereas eosinophilia occurred in two and possibly five of the remaining six patients. A fall in monocyte count occurred only in case 3. All of the survivors showed an initial monocytosis. In four of the patients reported in this article, a definite increase in subsequent monocyte counts was noted and, in two others, there was an increase of probable significance. Three patients showed an early rise in erythrocyte count and hemoglobin level. One fatally injured patient and two survivors showed a moderate fall in red blood cell count. The relative anemias in the survivors were mild, and one was of questionable significance. Except for case 3, there was no decrease in the reticulocyte counts, but four and possibly five patients showed a fall in platelets.

It was pointed out that caution must be used in comparing directly the hematologic response of these patients with that reported in human subjects exposed to radiation under other conditions. Thus, certain tissue reactions (prompt death of the tissues of the hand of cases 1 and 3, and partial protection of the bone marrow of all cases) are unique in the present situation and may be expected to modify the hematologic reaction usually seen in the acute radiation syndrome.

C. *Cytologic Changes in the Blood Cells*

1. *Lymphocytes*

Lymphocytes showing varying degrees of disintegration were noted in the peripheral blood of the fatally injured patients. The lymphocytes of case 4 showed minor cytologic changes, whereas those in the other survivors appeared entirely normal. Many of the degenerative changes seen in the circulating lymphocytes could also be observed in the histologic sections of tissue lymphocytes. These changes consisted of cellular enlargement, clumping of the chromatin, vacuolation of both nucleus and cytoplasm, and some instances of nuclear pyknosis. It is interesting to note that a particular type of change could be confined to one part of the nucleus. Thus, part of the nucleus of some cells was pyknotic or poorly stained, while the rest of the nucleus appeared relatively normal. Perhaps more remarkable than the state of disintegration of cells was the presence of relatively normal lymphocytes in the blood of cases 1 and 3 just before death.

The type of degenerative changes noted in the lymphocytes of these patients was not reported in the Japanese patients. However, an abnormal type of lymphocyte, similar to that which occurs in infectious mononucleosis,

was seen in the blood films of the Japanese (Medical Report of Joint Commission, Section 6). These large cells contained variable amounts of cytoplasm and small eccentrically placed nuclei, the chromatin of which was coarse and bunched. In some cases these abnormal cells constituted 25 per cent of all circulating lymphocytes. Although a few cells with these characteristics were seen in the blood films of case 1, this type of cellular change was not conspicuous either in the fatally injured patients or in the survivors.

The increase in the number of refractive, neutral red-staining granules in the lymphocytes, noted in all but two patients, has been described previously in persons chronically or acutely exposed to ionizing radiation (Dickie and Hempelmann, 1947). A comparable change has been observed recently in a series of four patients with beta-ray burns (Knowlton et al., 1949). The increase in refractive granules does not appear to be a specific effect of ionizing radiation, for it is also observed in the lymphocytes of persons exposed to certain toxic chemicals. These intracellular inclusions are believed to be different from the neutral red-staining vacuoles also seen in supravitally stained cells. The neutral red bodies are not seen in blood smears fixed with alcohol since they are soluble in alcohol. Recent evidence indicates that the refractive bodies are lipid in nature and presumably contain a large proportion of phospholipids. They are birefringent, have a high refractive index, and are increased in numbers by the action on the living cells of the neutral red component of the supravital dyes (Hempelmann and Knowlton, in press). It should be pointed out that the increased number of refractive bodies persisted for more than two years in case 4 and for over one year in case 6.

2. Neutrophils

Degenerative changes which consisted of swelling and vacuolation of the nucleus and cytoplasm and pallor or pyknosis of the nuclei were observed in the neutrophils of the more severely injured patients. It is interesting to note that two types of disintegration could occur simultaneously in the same cell. Thus, the nucleus of a single cell might show swelling of one lobe and pyknosis of another.

The most interesting change in the neutrophils was the marked degree of toxic granulation of the cytoplasm. This appeared promptly (one hour after exposure in case 3), and lasted until the acute stage of the illness had passed. The granules were similar in appearance to those described in patients with severe infections. The granulation occurred in young and old cells alike, and the depth of staining of the granules was often accentuated by the pallor of the cell nuclei. The staining properties of the granules were not destroyed by incubating fixed blood films with crystalline ribonuclease. It has been suggested that these cells might be basophils (Jacobson, personal communication). If these granules had stained with metachromatic dyes, this view would have been established as fact. Since the metachromatic reaction did not take place in destained blood films of case 1, this possibility is still open to question.

3. *Monocytes*

The "lacy" type of nuclear vacuolation described in the monocytes of case 1 was not observed in the blood of the other patients in this series and has not been reported in the literature.

4. *Platelets*

The only morphologic change in the platelets was the increase in size observed in case 1.

5. *Summary*

Cytologic changes in the circulating leukocytes occurred only in the patients who had received the largest doses of radiation. The exception to this statement is the increase in neutral red-staining, lymphocytic granules which was apparent in almost all patients. The changes in cell structure were degenerative in nature and were consistent with those seen in fixed tissues.

D. *Bone Marrow Response as Revealed by Sternal Marrow Aspirations*

It is impossible to get a satisfactory picture of the sequence of events in tissue destruction and repair from a study of the limited number of bone marrow aspirations done on this series of patients. Therefore, the pattern of the response of the bone marrow observed in the Japanese patients will be presented briefly (Medical Report of Joint Commission, Section 6), to be used as a basis for the interpretation of the observations on these patients.

The early response of the bone marrow in the irradiated Japanese was not studied thoroughly, but enough observations were made to show that destruction of marrow occurred promptly. In the single specimen obtained from a fatally injured patient on the second day after exposure, 5 per cent of the marrow cells were lymphocytes, 29 per cent histiocytes, 19 per cent plasma cells and 44 per cent unidentifiable. In a few other marrow specimens, obtained several days later, only a few plasma cells, degenerating metamyelocytes and small lymphocytes were observed. In contrast to the early destruction, all specimens obtained seven to 10 days following exposure showed regeneration of the reticular cells. Foci of mononuclear cells gradually appeared in the hyperplastic reticulum. There was a gradual metamorphosis of the reticular marrow into cells of the granulocytic, lymphocytic, erythrocytic and megakaryocytic series. Erythrocytic regeneration was delayed longer than was the recovery of the leukocytes. In most cases the pattern of myelopoiesis was normal seven or eight weeks after exposure, whereas maximal erythropoiesis did not occur until the tenth to twelfth week. Samples of the bone marrow of the survivors appeared completely normal between the twelfth and sixteenth weeks and thereafter.

Early destruction was evident in the heavily irradiated sternal marrows of cases 3 and 4, with only a few viable cells seen on the second day after exposure. In contrast, cases 7 and 9 showed no evidence of damage of the marrow on the fourth day after the accident. The most revealing studies are those done by Dr. Carl V. Moore on specimens obtained from cases 4

and 6 twenty-two days after exposure. His observations indicate that there was marked hypoplasia of the marrow in both cases, with only a few islands of normoblasts in case 4 and a predominance of normoblasts in case 6. The marrow of the latter patient also showed a striking increase in the number of phagocytic myelocytes and a moderate increase in tissue basophils. Hyperplasia of the reticulum was not observed. The marrow specimens of cases 4 and 6 obtained during the eleventh week showed a normal cellular pattern, even though the erythrocyte count of the circulating blood was still depressed at this time. In evaluating the studies of the bone marrow, it must be recalled that the sternal tissues of these patients were subjected to the full impact of the neutron irradiation. Nevertheless, it is evident that the present findings bear out the observations on the Japanese of rapid destruction of marrow within two days and regeneration within three months. They do not show the reticular hyperplasia noted in the Japanese.

Studies of the bone marrow response of animals show that cellular destruction occurs shortly after exposure and that recovery is also relatively rapid (Bloom, 1948; Lawrence, Dowdy and Valentine, 1948). In rabbits given 800 roentgens of x-rays, cellular damage is evident 30 minutes after exposure and is marked three hours later (Bloom, 1948). The erythroblasts disappear more rapidly than the granulocytes. Destruction of tissue reaches its maximum five days after exposure, following which an "abortive" attempt at regeneration occurs, first in granulopoiesis and then in erythropoiesis. Sustained erythropoiesis begins on the tenth to fourteenth day, while myelopoiesis is somewhat delayed. In rabbits receiving smaller doses of x-rays (400 roentgens), the bone marrow damage is not so extensive or prolonged and the precursors of the granulocyte recover before the erythroblastic cells.

E. *Disturbance of the Blood Clotting Mechanism*

Studies of blood coagulation in the patients involved in the second accident show that the blood clotting time was prolonged considerably in cases 3, 4 and 6. The prothrombin time remained normal in all patients except case 3, who showed a terminal fall. The clotting time increased progressively in case 3, until at death whole blood samples were uncoagulable. The maximal disturbance in blood clotting in the case of the survivors occurred on the sixth day after exposure. The clotting time could be brought back to normal in all cases by adding small amounts of toluidine blue to the sample of whole blood.

The increase in the clotting time of the blood of irradiated persons and animals has been attributed, in part, to the presence of a material in the circulating blood which has been said to be heparin-like in nature (Allen et al., 1948). The excess of this material can be neutralized by toluidine blue or protamine sulfate, and the clotting time brought back to normal in vitro or in vivo, even in the presence of severe thrombocytopenia. This is evidence in favor of the heparin-like character of the anticoagulant, since toluidine

blue, a metachromatic dye, is known to combine specifically with the sulfuric acid ester type linkage such as is possessed by heparin. The possible relation of this circulating anticoagulant to the tissue mast cells is discussed in Section IX.

It should be emphasized that prolongation of the clotting time is not a constant finding in animals and, if it occurs, is not always neutralizable with toluidine blue. Furthermore, increased clotting time is only one cause of bleeding in the acute radiation syndrome (Cronkite, 1950). The decrease in platelets and the increased capillary fragility, both of which have been observed in the injured Japanese and in irradiated animals, obviously contribute to the development of the clinical bleeding which is usually so conspicuous several weeks after exposure to lethal doses of radiation. These three phenomena appear to be unrelated. This is suggested by the fact that the appearance of the anticoagulant in irradiated dogs does not always coincide in time with the development of the thrombocytopenia (Allen et al., 1948). In a report on the hemorrhagic phenomena in the animals exposed to the atomic explosions at Bikini, three types of bleeding were noted at different times after exposure: Capillary fragility with scattered petechiae occurred early, thrombocytopenia with purpura appeared later in the illness, and prolongation of the clotting time with severe bleeding was observed only during the terminal stages of the illness (Cronkite, 1947).

SECTION VII. CHEMISTRY OF THE BLOOD AND URINE

A. Chemistry of the Blood
1. Quantitative Changes in Blood Chemistry
a. Sodium and chloride ions
b. Calcium
c. Non-protein nitrogen and urea
d. Uric acid
e. Total and fractionated serum protein
2. Electrophoretic Pattern of Plasma Proteins
3. Summary
B. Chemistry of the Urine
1. Corticoid-like Fraction
2. Urobilinogen
3. Porphyrins
4. Urorosein
5. Amino Acids
6. Potassium
7. Summary

VII. CHEMISTRY OF THE BLOOD AND URINE

Prior to the last war, the medical literature concerned with the changes in blood and urine chemistry induced by exposure to radiation was limited to conventional metabolic studies. Much of the data is controversial, as can be seen in the review of this subject by Dunlap (Warren, 1942). As

will become evident, some of the inconsistencies may be explained by the fact that many of the chemical responses appear to be biphasic in nature; the reported data depend, therefore, not only upon the magnitude of the dose of radiation but also upon the time after exposure at which the studies were made. The extensive chemical investigations of the blood and urine in irradiated human subjects and animals carried on during the last six years will soon be published in the Plutonium Project Report. Some of these studies have appeared in articles by Schwartz (1947, 1949).

A. *Chemistry of the Blood*

1. *Quantitative Changes in Blood Chemistry*

The methods used in studying the blood chemistry of these patients are standard procedures which can be found for the most part in the book, *Laboratory Methods of the U. S. Army* (Simmons and Gentzkow, 1946). Except for the definite changes noted in case 3, the results of the rather limited studies do not signify a serious disturbance in the chemistry of the blood of these patients. Where deviations from the norm occur, the changes are small and the significance is dubious. However, when the data from all patients are collected in a single chart (page 441), certain conclusions can be drawn concerning the change or lack of change in the blood chemistry in persons receiving large doses of radiation.

a. *Sodium and chloride ions*

A slight fall in serum sodium and low level for whole blood chlorides occurred in case 3. The slight and questionably significant drop in the sodium level was evident during the first few days of the illness before large quantities of fluid and electrolytes were lost as a result of gastric suction. The blood chlorides decreased during the last few days of the illness despite efforts to maintain the normal electrolyte level by parenteral saline administration. In the other patients, the studies of serum sodium and blood chlorides were insufficient to permit a good evaluation of the true state of the electrolyte balance. Nevertheless, there appeared to be no significant change in these patients, as is shown by the normal chloride level of cases 4 and 6, and the low normal values for serum sodium in the same patients during the first few days after exposure.

The observation of decreased serum sodium in case 3 is unlike that obtained in recent studies of irradiated rats, in which retention of sodium in the blood and tissues was observed (Bennett, Bennett and Howland, 1949-a). Studies on patients receiving radiation therapy, however, show decreased blood chlorides even though chloride retention in tissues occurs (Dunlap, Warren, 1942). Similarly, a progressive decrease in blood chlorides and sodium often may be demonstrated during the first few days after injury in thermally burned patients (Harkins, 1942).

Disturbances in body sodium of the most severely injured patient in the present series are not unexpected in view of loss of intestinal fluids and the extensive adrenal damage which is known to have occurred. The rather

slow fall in serum sodium in case 3, however, is unlike the immediate drop in chlorides, and presumably sodium, noted in the *general adaptation syndrome* or *alarm reaction*, which occurs as a result of many nonspecific stimuli of which roentgen-rays are allegedly one (Selye, 1940, 1946).

b. *Calcium*

The calcium content of the blood was studied only during the terminal phase of the illness of case 3. A decreased calcium value is usual in a patient with uremia of this degree. It is undoubtedly the result of phosphorus retention which, although not measured, must have been a consequence of the impaired renal function in this patient.

c. *Non-protein nitrogen and urea*

Severe nitrogen retention was observed in case 3. This was compatible with the degree of kidney damage seen at autopsy. In case 1, however, the only determination of blood urea gave a value at the upper limit of normal on the fourteenth day. One can only speculate as to whether azotemia occurred in the terminal week of life of this patient. In view of the good output and continued high specific gravity of the urine and the absence of significant kidney lesions at autopsy, it seems unlikely that true or even extrarenal nitrogen retention of a serious degree occurred in this patient. The determinations of blood urea and non-protein nitrogen on the survivors of the second accident were done often enough to indicate that azotemia did not occur.

Increased excretion of non-protein nitrogen in the urine after abdominal irradiation of dogs was first demonstrated many years ago (Hall and Whipple, 1919). The animals which received lethal doses of x-rays usually showed no elevation of the blood non-protein nitrogen until shortly before death. Recent studies on dogs subjected to lethal doses of total-body irradiation indicate an actual decline in blood non-protein nitrogen until 48 hours before death, when a pronounced rise occurs (Prosser, Painter and Swift, 1947-b). In contrast to the delayed nitrogen retention observed in the terminal stages of injury by ionizing radiation, patients with severe thermal burns may show an elevated blood urea within several hours after injury (Medical Research Council, 1944).

As pointed out previously, the mild negative nitrogen balance shown by thermally burned patients (Section V) is not believed to be due to enhanced excretion of breakdown products of protein but rather to reduced caloric intake. In irradiated dogs, on the other hand, the negative nitrogen balance is presumed to be due, in part, to increased tissue breakdown. In case 3, the disproportion between the non-protein nitrogen and urea on successive days is interesting, since observations on irradiated dogs indicate that during the terminal azotemia the ratio of these nitrogen fractions is unchanged (Prosser, Painter and Swift, 1947-b). In patients with thermal burns, however, an increase in the non-urea nitrogen fraction of the blood similar to that in case 3 is said to be not uncommon (Taylor et al., 1943). One of the non-urea fractions responsible for the azotemia is called "residual nitro-

gen." This substance has not been characterized completely, but an idea of its composition can be gained from the fact that it breaks down on hydrolysis to form amino-nitrogen and amido-nitrogen.

d. *Uric acid*

A terminal increase in the blood level of uric acid was noted only in case 3. No attempt was made to follow the amounts of uric acid excreted in the urine, which might have given a better indication of a disturbance in purine metabolism. An increase in amount of urinary uric acids has often, but not invariably, been reported to occur in patients following radiation therapy (Pohle and Sevringhaus, 1930). In dogs which had received a lethal dose of x-rays, a terminal rise in urinary uric acid was observed, but in these same animals, no significant change was noted in the excretion of allantoin (Schwartz, 1949).

e. *Total and fractionated serum proteins*

The quantitative data for total and fractionated serum proteins in the present series of patients are difficult to interpret. There is no obvious trend or change in pattern. All of the patients injured in the second accident showed an increased value for serum proteins on the eighth day after exposure, due to an elevation of the globulin fraction. This observation was not confirmed immediately, so it is not possible to be certain that this represents a true increase.

Data gained from the study of irradiated dogs indicate that a slight decline occurs in the plasma protein level during the first week after exposure (Prosser, Painter and Swift, 1947-b). In dogs receiving more than 300 roentgens of x-rays, a rise up to 15 per cent of the total circulating proteins occurred during the second and third weeks. Those animals which died showed a terminal decline in protein values following the initial rise. The infrequency of the protein determinations in the present patients makes it impossible to ascertain whether such a biphasic response occurred.

In patients with thermal burns, an increase in serum proteins may occur within the first few hours after injury (Cope et al., 1948). Later, the protein level may fall below normal values, particularly in cases receiving inadequate therapy in the form of transfusions of whole blood or plasma.

2. *Electrophoretic Pattern of Plasma Proteins*

The electrophoretic pattern of five heparinized blood samples from these patients was determined in a Tiselius apparatus (Tiselius, 1937), using the Schlieren scanning technic (Longsworth, 1939). The resultant ascending patterns of the patient's plasma proteins, as well as those of six control samples, were analyzed by measuring with a planimeter the area under each peak in the curve. The proportion of protein in the albumin fraction and in each of three globulin fractions is shown in the accompanying table (page 444). Significant changes in the plasma proteins were found only in case 3. Here the plasma albumin level diminished, while an increase in the alpha globulin fraction occurred. This change in the electrophoretic pattern is

shown in figures 18 and 19. Minor changes of questionable significance were also found in the electrophoretic patterns of case 6.

Changes have been described in the electrophoretic pattern of plasma proteins in dogs given large doses of x-rays (Muntz, Barron and Prosser,

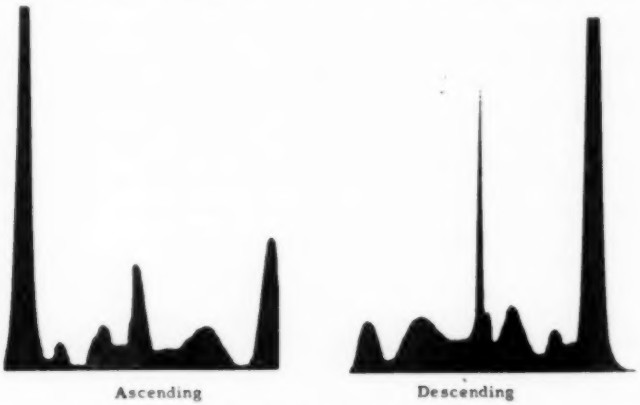


FIG. 18. Normal human plasma protein pattern.

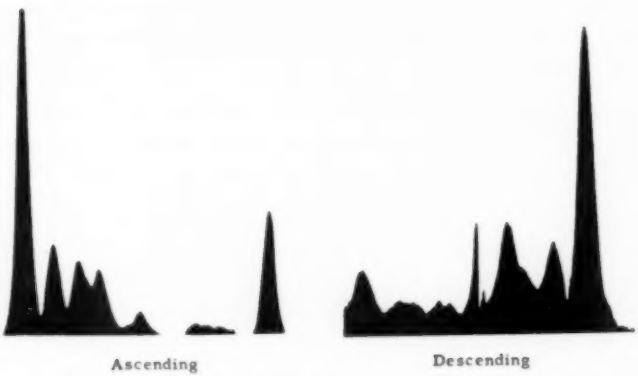


FIG. 19. Plasma protein pattern of case 3 seven days after exposure.

1949). These changes consisted of an increase in the alpha globulin fractions of the plasma and a diminution of the albumin fraction. The increase in globulin coincided in time with the development of fever in severely injured animals. A similar change in the electrophoretic pattern has been observed in dogs poisoned with sulfur mustard (β-β-dichlordiethyl sulfide) and injured in other ways, including thermal burns (Gjessing and Chanutin,

1946; Chanutin and Gjessing, 1946). A marked increase in the alpha globulin fraction has also been observed in human beings with pneumonia and other febrile diseases (Blix, 1939).

It seems probable that the changes in plasma protein observed in case 3 are not specific for radiation damage. It has been suggested that the close resemblance between the protein changes in severe bodily injury and in acute febrile infections may indicate that the reaction of the plasma proteins to injury is related to adrenal stimulation and protein catabolic response (Luetscher, 1947).

It should be pointed out that the electrophoretic method of analyzing proteins is more accurate and reproducible than the "salting out" method usually used in fractionating proteins (Luetscher, 1947). The results determined by this method are undoubtedly more reliable than the protein fractions and albumin : globulin ratios reported in the table (page 441).

3. *Summary*

Omitting the first two cases from the discussion because of inadequate study, the changes in blood chemistry may be summarized by saying that significant abnormalities were demonstrated only in case 3, and even here were not of a sufficient degree, in themselves, to be the immediate cause of death. These changes consisted of a gradual fall in serum sodium and whole-blood chlorides, a slight elevation of uric acid, a terminal rise in nitrogen associated with a depressed calcium level, and a modification of the plasma protein (decreased albumin and increased alpha globulin fraction). Such changes are consistent with those noted in animals given lethal doses of ionizing radiation. The limitations of this study are such that minor variations in the blood chemistry in the survivors probably would not have been detected.

B. *Chemistry of the Urine*

Except for small aliquots used for clinical microscopy and radioactivity studies, all of the urine collected from the patients involved in the second accident was sent to the Argonne National Laboratory in Chicago for analysis. The 24 hour pooled samples under toluene were sent via air express after careful packaging and refrigeration with dry ice. In all instances, however, the dry ice had evaporated by the time the samples reached Chicago, so that the urines were unchilled at least part of the time in transit. Upon being received at the Argonne Laboratory, quantitative analyses of the corticoid-like substances, urobilinogen and porphyrins were undertaken promptly. The remainder of the urine samples were stored in an icebox at 40° F. Analysis of urinary amino acids was started one year later, and determinations of potassium content of the samples were made three years later.

1. *Corticoid-like Fraction* *

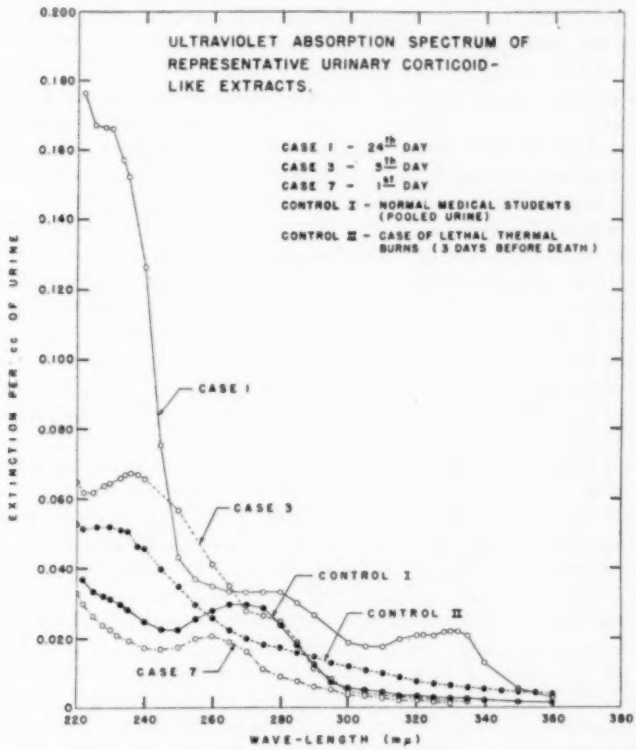
Studies of the urinary corticoids are of interest because abnormalities in quantity may indicate dysfunction of the adrenal cortex such as is known to occur after trauma or other forms of stress (Selye, 1940, 1946). Abnormally large quantities of corticoids have been shown to be excreted by patients who have been operated on or who have suffered severe thermal burns (Shipley et al., 1946). In one thermally burned patient of that series, the urinary corticoid level was elevated for more than 12 days. Chemical studies of corticoid-like urinary extracts also have shown increased excretion levels in patients with thermal burns (Talbot et al., 1945). Investigation of neutral 17-ketosteroid excretion which, although a poor measure of adrenal activity, is nevertheless influenced by adrenal cortical function, also brings to light some interesting abnormalities in patients with thermal burns (Aub et al., 1943). Thus an increased excretion of neutral 17-ketosteroids occurs from three to seven days after injury, following which the urinary content of this steroid falls precipitously to low normal or subnormal levels. The duration of the depressed 17-ketosteroid level is said to be correlated with the severity of the injury and the period of convalescence (Aub et al., 1943). A recent report indicates that patients with ankylosing spondylarthritis show an increased 17-ketosteroids excretion after receiving x-ray treatment (Davison, Koets and Kuzell, 1949). Irradiated dogs also are said to show an initial increase in urinary 17-ketosteroids, followed by a fall to subnormal values five to 12 days after exposure (Lawrence, 1949).

The investigation of corticoid-like materials in the urine of the present patients was patterned after the colorimetric method of assaying urinary extracts (Talbot et al., 1945). This method employs the measurement of the reducing properties of a ketonic water-soluble lipid component of urine which is believed to be composed largely of the corticosteroids. Circumstances did not permit complete extraction and purification of the corticoid fraction of the urine samples in the present series of cases. Also, the procedure was modified somewhat from that originally reported, in that spectrophotometric analysis rather than colorimetric assay was used for the quantitative determination of the excretion products. The method of separation of the corticoid-like fraction consisted, in brief, of extracting urine aliquots several times with chloroform and benzene. The crude extract was not

* Since the terminology in the field of adrenal cortical hormones has not been agreed upon, it seems advisable to define the terms as they are used in this article. The following definitions have been suggested by Dr. L. L. Engel (personal communication). The term *cortin* refers to adrenal cortical extracts which have the "total" biologic activity of the adrenal cortical hormones. *Corticoid*, on the other hand, is applied to urinary extracts which have "some" of the biologic properties of cortin. The tautologic term *corticoid-like* is used to describe those urinary substances which are presumed to be corticoids because of similar chemical and physical properties, but which have not been identified by biologic assay methods. *Corticosteroid* refers to the cortical hormones, the chemical structure of which is known, e.g., corticosterone, compound E, etc. (See Fieser and Fieser, 1949, for a discussion of the chemistry and physiological properties of the adrenal cortical hormones.)

separated further into ketonic and nonketonic fractions. Its absorption pattern in methanol was determined by use of a Beckman spectrophotometer.

The ultraviolet absorption pattern from 220 to 340 mμ (millimicrons) of the crude extract of several selected urine samples is shown on this page. It is evident from this graph that there is an increase in specific absorption in the region of 230 mμ in the urine extract of case 3 and of a thermally



burned patient. In other samples from severely injured patients of the present series, not shown on this graph, there was a plateau or actual peak at about 230 mμ, similar to that noted in case 3. The adrenal cortical hormones, e.g., corticosterone, show specific absorption in this region of the ultraviolet spectrum due to the presence of alpha, beta unsaturated ketones in their chemical structure (Fieser and Fieser, 1949). Because of the method of extraction, it seems possible that the absorbing materials measured in this study are composed, at least in part, of the corticoid-like

water soluble reducing substances measured by the colorimetric method of Talbot.*

In an effort to show the disturbance in the absorption pattern in the 230 mμ region, figures are given on the composite chart (pages 443 and 444) and in individual case histories to indicate the slope of the curve from 220 to 240 mμ (a) and from 240 to 260 mμ (b). The greater the absorption at 230 mμ, the steeper will be the slope from 240 to 260 mμ, or the larger is the ratio of 240/260. Similarly, abnormalities in the curve will be reflected in the ratio a/b. No effort is made to express the absolute amounts of absorbing material.

Examination of the composite chart indicates an increase in absorption at 230 mμ for cases 1, 3, 4 and 6. This increase was most marked in the single urine specimen of case 1 obtained shortly before death. In case 3 it was less marked and inconstant, falling almost to normal on the second and again on the eighth days after exposure. In this case, however, as well as in cases 4 and 6, the greatest increase occurred between the fifth and seventh days after exposure. Disturbance of absorption in the 230 mμ region was still observed in the urine of case 6, obtained three weeks after the accident. In contrast to the observations on these patients, the absorption pattern of the urine of the less heavily exposed patients (cases 7 to 10) was normal. Studies in these latter cases, however, were limited to one determination on urine samples passed immediately after the accident. It is possible that observations on later specimens might have shown an abnormal ultraviolet absorption curve.

It must be emphasized again that the ultraviolet absorbing substance measured in these studies may not be a single compound, and that there is only circumstantial evidence indicating that it is similar to the reducing substance measured by colorimetric assay. It seems possible, however, that the two substances are similar in nature or at least are composed of some of the same steroids. The reducing substance measured colorimetrically by Talbot has been found to be elevated in patients with adrenal hyperfunction and is believed, therefore, to be composed of corticoids. It might be expected that the excretion of increased amounts of the material which absorbs light at 230 mμ in these cases also was the result of hyperactivity of the adrenal cortex. This would fit in with the Selye concept of the adaptive reaction of the body.† The terminal decrease in case 3 in the excretion of

* In a single patient receiving ACTH, strong absorption in the 230 mμ region has been demonstrated in the chloroform soluble fraction of the urine (L. L. Engel, personal communication). However, an increase in other steroids containing the alpha beta unsaturated configuration, testosterone, for example, if excreted could also be responsible for the absorption pattern noted in the present cases. In the absence of more specific chemical data, one can only suspect that some of the absorbing substances were corticoids because of the associated clinical findings.

† The clinical picture of the *general adaptation syndrome* or *alarm reaction* caused by injurious agents of various types has been clearly described, and its association with hyperplasia and hyperfunction of the adrenal cortex has been stressed (Selye, 1940, 1946). More recently, the clinical findings have been correlated with the release of adrenocortical hormones (Albright, 1943; Albright and Reifenstein, 1948). As this hypothesis helps to explain

this substance, if it is a corticoid, would be expected in view of the clinical circulatory collapse of this patient. There was no evidence in these studies to indicate late adrenal hypofunction, which some of the clinical symptoms of case 4 (asthenia and salt hunger) might suggest.

2. *Urobilinogen*

Although admittedly not a specific test for liver damage, the quantitative studies on urobilinogen excretion were used in this study as an index of liver function (Watson, 1942). Increased excretion of urobilinogen is also found in conditions other than liver injury; for example, abnormal amounts of fecal urobilinogen (as well as a less marked elevation of urine urobilinogen) are found in patients with enhanced hemolysis (Steigmann and Dyniewicz, 1943).

The method employed for determination of urobilinogen in urine was that devised by Schwartz, Sborov and Watson (1944). Before the results of these determinations are considered, it should be pointed out that all values in the present study may be low because of improper preservation of the specimens. Taking the figures at their face value, however, it is evident that abnormally high urobilinogen excretion was detected only in cases 3 and 4. The elevation in case 3 presumably occurred as a result of terminal liver failure (and possibly hemolysis). The urobilinogen level in case 4 was high only on the sixth day after exposure. Although no quantitative determinations were done in case 1, dilution tests and the incidental observation of strong absorption in the ultra-violet spectrum at 490 mμ (noted in the study of the urorosein content of a urine sample two days before death) suggest that the urobilinogen excretion also was high in this patient.

the urinary corticoid-like findings in this part of the chemistry discussion, it is reported briefly here: The adrenal cortex normally secretes, among others, two types of steroid hormones: (1) the nitrogen or "N" hormones, and (2) the sugar or "S" hormones. The "N" hormones which have testosterone-like properties and which are excreted in the urine as 17-ketosteroids, stimulate the synthesis of protoplasm. The "S" hormones, which have a profound influence on fat and protein, as well as on carbohydrate metabolism, supposedly inhibit anabolism. Thus, the action of these two hormones is, in part, antagonistic. The "S" hormones are composed of 11-oxy-corticosteroids, the metabolic products of which are presumed to have been measured in the urine of the patients of the present series, as well as in those mentioned in the literature (Shipley et al., 1946; Talbot et al., 1945).

The Albright hypothesis of the mechanism of the adrenocortical response to injury suggests that, following body trauma of any kind, release of both the "N" and the "S" hormones takes place. The increase in production of the "N" hormones is of a temporary nature and is soon followed by a decrease which lasts until convalescence is nearly completed. The resultant excretion of 17-ketosteroids, then, is first increased and later diminished to subnormal levels. The enhanced production of "S" hormones persists until convalescence, thereby accounting for the increased urinary excretion of 11-oxy-corticosteroids which Albright believes the urinary corticoids to be. This imbalance of adrenal cortical function with excessive secretion of "S" hormone, according to Albright, may account for the following symptoms noted after injury; leukocytosis, atrophy of lymphoid tissue, insulin resistance, muscular weakness, retarded growth and decreased synthesis of protoplasm in general. The adrenal response, as well as it can be reconstructed from the data in these cases and in irradiated animals, conforms to the general overall pattern described by Selye and Albright. The reader is cautioned, however, against placing too much emphasis on any single type of response of this nature; rather, one must keep in mind the numerous direct and indirect factors mentioned in Section IV in order to understand the complete clinical picture of the acute radiation syndrome.

It should be emphasized again that, in evaluating the urobilinogen determinations, one must keep in mind the probable destruction of this compound in the urine specimens due to lack of refrigeration. Therefore, minimal changes in liver function probably would not have been detected. Nevertheless, terminal liver failure and the associated increase in excretion of urinary urobilinogen observed in the fatally injured patients are consistent with the data obtained from dogs given lethal doses of x-rays (Schwartz, 1949), and with the observations in Japanese patients of increased urinary urobilinogen (as shown by qualitative tests) and other laboratory evidence of liver dysfunction (Medical Report of Joint Commission, Section 2). The questionable temporary increase in urobilinogen and possible associated liver dysfunction in case 4 are also compatible with the observations on dogs given sublethal but large doses of x-rays (Schwartz, 1949).

In thermally burned patients, increased excretion of urobilinogen may also occur during the first few days after injury (Medical Research Council, 1944).

3. *Porphyrins*

Disturbance in porphyrin metabolism is found in a number of apparently unrelated diseases; thus, increased amounts of urinary porphyrin may be found in patients suffering from liver disease, certain types of anemia, metal poisoning, febrile diseases of various types or congenital porphyrinuria (Watson and Larson, 1947). Of the two naturally occurring isomers of coproporphyrin, Type I predominates in normal urine, while either isomer (Type I or Type III) may appear in abnormally large quantities in the above mentioned diseases. Usually the Type III isomer predominates in the urine of patients with metal poisoning and with chronic liver disease.

A quantitative fluorimetric method of determination was used to study the urinary porphyrins of the present patients (Schwartz et al., 1947-a). It is apparent from the examination of the data in the composite chart (page 442) that the upper range of normal coproporphyrin (4 to 9 micrograms per cent or 30 to 100 micrograms per day) was exceeded in the single specimen from case 1. Also, increased porphyrin excretion was found in the urine passed by case 3 after the fifth day following exposure, and in the urine samples passed on the second and fifth days by case 4. In practically all urine samples from the other patients involved in the second accident, the levels of coproporphyrin were within the limits of normal. The only instances of depressed urinary coproporphyrin were found in the first two specimens of case 3, passed within 12 hours after exposure. Only two urine samples were fractionated into porphyrin isomers. In each case, Type III coproporphyrin predominated. Thus, in the urine sample of the first day of case 3, 77 per cent of the total porphyrin was Type III, while in pooled samples of the urine passed by case 4 during the first 12 days, 95 per cent of the pigment was Type III.

The terminal elevation in the level of the urinary coproporphyrin of the fatally injured patients is consistent with the observations on dogs given lethal doses of x-rays (Schwartz, 1949). It has been postulated that liver failure is responsible for the late increase in excretion of coproporphyrin. In heavily irradiated dogs the terminal increase is preceded by a depression of urinary porphyrin. This response, which could be due to the inhibition of erythropoiesis noted histologically, also occurred in case 3.

4. *Urorosein*

Urorosein is a red pigment formed in strong acid solution by the oxidation of indolacetic acid, a tryptophane metabolite excreted in the urine. The urorosein content of the urine specimens of these patients was determined using a procedure the exact details of which are given elsewhere (Schwartz, 1949). Relatively slight changes in urorosein and other pigments were found only in the two fatally injured patients. Since the urinary urorosein content seems to be related to the nutritional state, it is not surprising to find only mild changes in the excretion of this compound in these acutely ill patients who were previously in good health. In contrast, a marked increase in urinary pigments after irradiation has been observed in chronically ill patients who were undernourished at the time of radiation therapy (Schwartz, 1949).

5. *Amino Acids*

A quantitative determination of the individual amino acid content of the urine samples was made by paper partition chromatography according to the scheme developed by Dent (1946-b). The individual amino acids were identified by comparing their positions on filter paper with those of a synthetic mixture of pure amino acids studied simultaneously with the same solvents. A rough quantitative estimate was made by matching the intensity of the color of the ninhydrin reaction used to demonstrate the presence of the urinary amino acid with that of known amounts of pure amino acids. Although these studies were carried out on urine samples which had been kept for more than a year at 40° F., the consistent results of determinations made on the same specimens over a period of several months suggest that no marked loss of amino acids had occurred.

Studies of the amino acids in the urine of normal persons by partition chromatography show measurable quantities of glycine and alanine, as well as traces of leucine and valine (Dent, 1946-a). The analysis of the urine of healthy people used as controls in the present study largely confirms this finding. However, in addition to the four amino acids already mentioned, traces of taurine were noted consistently and, occasionally, small amounts of other amino acids were detected in highly concentrated urine samples. In contrast to these findings in normal subjects, many amino acids were demonstrated in considerable quantities in the urines of cases 3 and 4, and in a single specimen from case 1. In these cases the following amino acids were identified: cystine (as cysteic acid), aspartic acid, serine, glycine, taurine, alanine, valine, leucine, hydroxyproline, arginine and phenylalanine.

Two amino acids were not completely identified but may have been alpha-amino-n-butyric acid and tryptophane.

The quantities of individual amino acids in the urine specimens of the heavily irradiated patients following exposure varied from traces to 3 mg. of taurine per milliliter of urine in the sample passed by case 1 the day before his death. In cases 3 and 4, whose urinary output of amino acids was closely followed, the pattern of excretion was similar. In each case, abnormal amounts of amino acids were observed in the urine sample collected during the first day following exposure. The degree of amino-aciduria increased, reaching a peak on the sixth day after exposure in both cases. The amount of urinary amino acid was diminished in the specimen of the ninth day of case 4. After the twelfth day following exposure, the amino acid content of his urine decreased rapidly, although traces of abnormally occurring amino acids were still evident during the fourth week after exposure. Besides the sustained amino-aciduria in these two patients, an inconsistent increase of individual amino acids was noted in the other survivors of the second accident shortly after exposure. Thus, measurable quantities of four amino acids were demonstrated in the sample of case 8 six hours after exposure.

The amount of amino acids excreted in the urine of normal persons depends largely on the diet and on other factors in patients suffering from certain diseases. In healthy persons it has been shown by microbiologic assay that, of eight amino acids studied, 2 to 6 per cent of the total quantity ingested as protein was excreted in the urine (Sheffner, Kirsner and Palmer, 1948). A marked increase in the quantity of urinary amino acids has been demonstrated in a patient with liver damage (Uzman and Denny-Brown, 1948) and in patients with Fanconi's syndrome (Dent, 1947). In the former case, the inability of the damaged liver to deaminate plasma amino acids, or possibly a deficiency in the basic amino acid metabolism, was assumed to be the most likely cause of the amino-aciduria; in Fanconi's syndrome, on the other hand, a lowered renal threshold for amino acids and other plasma constituents has been demonstrated to be the probable etiologic factor. In neither instance was the degree of amino-aciduria so marked as in the present cases. In contrast to that observed in these pathologic states, amino-aciduria has not been observed in patients with thermal burns (Taylor et al., 1943-b).

The significance of the amino-aciduria in these patients with the acute radiation syndrome is not entirely clear. There is no reason to suspect a lowering of the renal threshold for clearance of amino acids, as has been shown to occur in the hereditary disease, Fanconi's syndrome. There is also experimental evidence which indicates that there is no defect in the ability of the liver of irradiated animals to deaminate amino acids or to incorporate them into liver protein. Thus, irradiated liver slices of mice were found to produce ammonia at a greater rate than normal (Crabtree, 1936). Also, the livers of irradiated mice and rats studied by in vitro as well as in

vivo procedures show an enhanced ability to incorporate tagged amino acids into protein (Altman et al., 1949; Hempelmann et al., 1950). These latter studies indicate that the skeletal muscle of irradiated animals has a decreased ability to incorporate amino acids into protein. Other experiments have demonstrated a partial inhibition of amino acid oxidation in the kidneys of

COMPOSITE CHART OF BLOOD CHEMISTRY

Case	Days After Exposure	Serum	Whole Blood					Serum				
		Sodium mEq./l	Chlorides mEq./l	Urea N mg. %	Non-protein Nitrogen mg. %	Uric Acid mg. %	Calcium mg. %	Icteric Index	Total Protein g. %	Albumin g. %	Globulin g. %	A/G
1	14	—	—	—	38	2.7	—	—	—	—	—	—
3	1 (1 hr.)	140	—	—	—	—	—	—	—	—	—	—
	2	134	75.3	10	—	3.4	—	—	—	—	—	—
	3	132	—	—	—	—	—	—	—	—	—	—
	4	133	67.8	—	57.0	—	—	—	5.4	4.1	1.3	3.1
	8	—	68.3	24	—	5.6	8.8	—	7.9	5.8	2.1	2.8
	9	—	63.0	—	161.0	—	9.4	70	7.0	4.8	2.2	2.2
4	1 (1 hr.)	139	—	—	—	—	—	—	—	—	—	—
	2	142	—	—	—	—	—	—	—	—	—	—
	3	136	78.3	—	—	4.0	—	—	—	—	—	—
	4	—	—	15	—	—	—	—	6.6	5.2	1.4	3.7
	8	—	80.9	7	—	3.9	—	—	9.6	5.3	4.3	1.2
	17	—	—	—	—	—	—	—	7.0	4.2	2.8	1.5
	21	—	—	—	—	—	—	—	7.0	4.7	2.3	2.0
	28	—	—	—	—	—	—	—	5.7	4.1	1.6	2.5
6	1 (1 hr.)	141	—	—	—	—	—	—	—	—	—	—
	2	138	—	—	—	—	—	—	—	—	—	—
	3	—	71.9	10	—	3.8	—	—	—	—	—	—
	8	—	80.9	14	—	4.4	—	—	8.0	4.5	3.5	1.3
	14	—	—	—	—	—	—	—	6.5	3.9	2.6	1.5
	19	—	—	—	—	—	—	—	6.9	4.5	2.4	1.8
	23	—	—	—	—	—	—	—	7.8	4.8	3.0	1.6
	27	—	—	—	—	—	—	—	6.8	4.8	2.0	2.4
7	1 (1 hr.)	140	—	—	—	—	—	—	—	—	—	—
	2	—	70.1	9	—	3.6	—	—	—	—	—	—
8	1 (2 hr.)	140	—	—	—	—	—	—	—	—	—	—
	3	—	84.8	8	—	3.2	—	—	—	—	—	—
9	1 (2 hr.)	141	—	—	—	—	—	—	—	—	—	—
	3	—	73.3	14	—	4.0	—	—	—	—	—	—
10	1 (1½ hr.)	138	—	—	—	—	—	—	—	—	—	—
	3	—	67.8	8	—	3.1	—	—	—	—	—	—
Normal values*		136–145**	77.0–85.6	10–15	25–35	2–4	10–12	4–6	6.5–8.0	4.0–6.0	1.5–2.5	2.1–3.1

* Table 24, p. 242, Simmons and Gentzkow, 1946.
** Serum sodium determinations done at Los Alamos Laboratory. For the normal range, see Mallory, Castleman and Parris, 1946.

animals injured by ionizing radiation (Barron, 1946). Such defects in utilization of amino acid, combined with the enhanced degradation of protein in the dead and dying cells, may be presumed to be responsible for the amino-aciduria observed in these patients.

6. *Potassium*

Quantitative studies of urinary potassium were carried out in the urine samples of cases 3 and 4 three years after the accident. Since the potassium intake of these patients is not known, it is impossible to draw definite con-

clusions about their potassium balance. However, the potassium excretion in case 4 was higher than that usually observed in healthy persons on a normal diet. The urinary potassium of case 3, however, was elevated only in the specimen of the sixth day following exposure specimen.

Although a high potassium intake could account for the elevated urinary level in case 4, the loss of weight in this patient suggests that the increased excretion was related, at least in part, to cellular breakdown. (See Section V.) His weight loss, about one pound a day, if due solely to breakdown of tissue, would be responsible for a daily output of 50 mEq. of urinary potassium. Since the caloric intake of this patient was not seriously reduced except during the first day and again from the fifth to the tenth days, it

COMPOSITE CHART OF URINE CHEMISTRY

Case	Days After Exposure	Volume (c.c.)	Specific Gravity	Corticoid-like Fraction			Coproporphyrin		Urobilinogen*	
				(a) 220/240 mμ	(b) 240/260 mμ	a/b	μg. %	μg./day	mg. %	mg./day
1	24			1.45	3.6	0.40	21	252		
3	1 (12 hrs.)	310	1.022	1.28	1.36	0.94	1.8	—	trace	—
	2	500	1.021	1.47	1.17	1.25	2.4	—	0.02	0.1
	5	990	1.027	0.93	1.62	0.57	18.8	186	0.06	0.6
	6	1,770	1.017	1.09	1.40	0.78	25.5	451	0.16	2.8
	7	466	1.016	1.70	1.18	1.44	25.1	117	1.33	6.2
4	1 (2 hrs.)	175	1.020				11.1			
	1 (4 hrs.)	160	1.012				2.0	52	trace	trace
	1 (15 hrs.)	660	1.020				4.5			
	2	1,825	1.022	1.40	1.32	1.06	19.8	362	0.01	0.2
	5	1,520	1.020	1.40	1.75	0.80	11.2	170	0.08	1.0
	6	1,390	1.020	1.07	1.95	0.55	10.1	140	0.48	6.7
	7	1,720	1.017				3.8	65	0.01	0.2
	8	1,710	1.016	1.43	1.58	0.90	2.5	43	0.01	0.1
	9	3,045	1.015	1.91	1.52	1.25	5.0	152	0.04	1.1
	10	1,795	—	—	—	—	—	—	—	—
	11	3,050	1.016	—	—	—	4.1	125	0.09	2.6
	18	2,200	1.013	1.62	1.06	1.53	1.6	35	0.01	0.2
	21	3,650	1.018	1.49	1.15	1.30	5.7	206	trace	trace
	24	2,780	1.020	—	—	—	2.4	67	trace	trace
	26	2,565	1.020	—	—	—	6.7	172	trace	trace
6	1 (4 hrs.)	134	1.020	—	—	—	2.5	—	trace	—
	1	630	1.020	—	—	—	4.3	—	trace	—
	2	435	1.030	—	—	—	5.7	25	trace	—
	5	2,660	1.015	—	—	—	1.6	42	trace	—
	6	3,050	1.015	0.92	2.63	0.35	4.2	128	trace	0.2
	7	2,815	1.010	—	—	—	1.8	51	trace	—
	8	1,760	1.012	—	—	—	5.5	97	0.04	0.7
	9	2,355	1.013	—	—	—	4.1	97	0.01	0.3
	10	3,300	1.010	—	—	—	1.9	63	0.02	0.7
	11	3,655	1.007	—	—	—	1.7	62	0.03	1.2
	12	2,585	1.015	—	—	—	2.6	67	0.01	0.36
	19	2,920	1.010	1.43	1.59	.090	2.9	85	trace	0.2
	21	1,880	1.020	1.32	1.87	0.71	1.3	24	trace	—
	26	2,730		—	—	—			0.03	0.9
	29	1,820		—	—	—			0.02	0.3

COMPOSITE CHART OF URINE CHEMISTRY—*Continued*

Case	Days After Exposure	Volume (c.c.)	Specific Gravity	Corticoid-like Fraction			Coproporphyrin		Urobilinogen*	
				(a) 220/240 mμ	(b) 240/260 mμ	a/b	μg. %	μg./day	mg. %	mg./day
7	1 (12 hrs.)	1,270	1.013	1.88	0.85	2.21	4.8	72	0.03	0.4
	1	310	1.015				3.1		0.01	
8	1 (12 hrs.)	115	—	1.72	0.98	1.76	—	—	—	—
	1	1,250	1.029	—	—	—	10.1	126+	0.02	0.3+
9	1 (4 hrs.)	171	1.016				7.5	—	trace	—
	1	870	1.017	1.97	1.07	1.84	2.3	—	trace	—
10	1 (4 hrs.)	128	1.015	—	—	—	3.2	—	trace	—
	1	1,285	1.011	1.88	1.08	1.74	1.9	24	trace	—
Patient with Thermal Burn	**			1.15	1.77	0.65				
	***			1.38	1.33	1.04				
Controls, usual range			1.015 1.030	1.5–1.7	0.9–1.1	1.4–1.8	4–9	30–100	trace to 0.2	trace to 2

* Urobilinogen values probably too low because of lack of complete refrigeration during trip to Chicago.
** Three days before death.
*** Day of death.

seems possible that at least some of the urinary potassium can be accounted for by degradation of protoplasm.

In thermally burned patients, the potassium balance is maintained except for a transient negative phase shortly after injury (Moore et al., in press). There is no correlation in cases of thermal burns between the potassium and the nitrogen balance. The latter is often negative for several weeks after injury.

7. Summary

The more heavily irradiated patients showed an increased excretion of a urinary substance or substances which have certain of the properties of corticoids and which are referred to arbitrarily as "corticoid-like." Increased amounts of coproporphyrin (mainly Type III) and urobilinogen were found in the urine of case 3, presumably as a result of liver damage. Mild transient changes in the excretion of porphyrin and urobilinogen of questionable significance were found in case 4. Minor changes in urinary urorosein were observed in cases 1 and 3. Amino-aciduria, presumably due to a decreased utilization of amino acids and possibly to increased protein breakdown, was pronounced in cases 1, 3 and 4. The potassium excretion of case 4 was higher than that usually observed in healthy people on a normal diet.

COMPOSITE CHART OF AMINO ACID EXCRETION

Amounts expressed in mg./ml. (approximate concentration)

Case	Day of Illness	Cysteic Acid	Aspartic Acid	Glutamic Acid	Glycine	Taurine	Alanine	Valine	Leucine	Unknown Below Alanine	Unknown Below Valine	Other
1	23	0.5	0.5	1.0	1.5	3.0	trace	0	0	0	0	hydroxyproline 1.5
3	1	0.1	0.1	0.1	1.0	0.75	0.5	0.25	0	0.25	0.1	phenylalanine 0.1
	2*	0	0.1	0.1	0.75	1.0	0.5	0.5	0	0.25	0	phenylalanine 0.1
	6	0	0.5	1.0	1.0	1.75	0.5	0.25	0.25	0.25	0	serine—tr. unknown—0.25 arginine—0.1
	7	0	0.5	1.0	1.0	1.0	0.25	0.5	0	0	0	—
4	6 hr.	0.25	0.25	0.5	1.0	0.75	0.25	trace	0	0	0	arginine—0.1
	1											unknown—0.1
	1	trace	0.25	0	2.5	0.75	trace	0.1	0.1	trace	0	unknown—0.25
	2	0	0.5	0.5	2.0	0.75	0.25	0.1	0.1	0.25	0	—
	4	0.1	0.25	0.5	trace	1.0	0	0.1	0	0	0	—
	6	0.25	0.5	0.75	1.5	1.0	0.25	0.1	0.1	0.1	0	arginine—tr.
	9	trace	0.25	0.25	0.5	0.5	0.25	0.1	0	0.1	0	—
	10	0.25	trace	0.1	0	0.75	0	trace	trace	0	0	—
	11	0.1	0.25	0.25	0.5	0.75	trace	0.1	0	trace	trace	—
	17	trace	0	0.25	1.0	0	trace	0	0	0	0	—
	20**	0.1	0.1	0.1	0	1.0	0	trace	0	0	0	—
	22	0	0	trace	0.25	0	0	0	0	0	0	—
	25	trace	0	trace	trace	0	0	0	0	0	0	—
	27	trace	0	trace	0	0	0	0	0	0	0	—
	30	0	0	trace	0	0.1	0	0.1	0	0	0	—
6	6 hr.	0	0	0	0	0	0	0	0	0	0	—
	1	0	trace	0	0	trace	0	trace	0	0	0	arginine—0.1
	6	0	0	0	0	0.5	0	0.1	0	0	0	—
	7	0	0	0	0	0	0	0	0	0	0	—
	8	0	0	0	0	0	0	0	0	0	0	—
	9	0	0	0	0	0	0	0	0	0	0	—
	11	0	0	0	trace	trace	0	0	0	0	0	—
	12	0	0	0	0	0	0	0	0	0	0	—
	20	0	0	0	trace	0	0	0	0	0	0	—
	23	0	0.1	0	0	trace	0	trace	0	0	0	—
	24	0	0	0	0	0	0	0	0	0	0	—
	30	0	0	0	trace	0	0	0	0	0	0	—
7	6 hr.	0	0	0	0	0.1	0	0	0	0	0	—
	1½	trace	trace	trace	0	0.5	0	0	0	0	0	—
8	6 hr.	0	0.1	0.25	0.25	trace	0.1	trace	trace	0	0	—
9	6 hr.	0	0	0	0	0.25	0	0	0	0	0	—
	1	0	0	trace	0.5	0.25	trace	0.1	0	0	0	—
10	6 hr.	0	0	0	0	0	0	0	0	0	0	—
	1	trace	0	0	0	0.25	0	trace	0	0	0	—
Controls 3 cases 8–24 hrs.		0	0	0	0.1–0.25	trace	trace 0.1	trace	trace	0	0	serine—tr. alanine—tr. arginine—tr.—0.1

* 12-hour sample. ** Partial 24-hour sample.

THE ELECTROPHORETIC PATTERN OF PLASMA PROTEIN

Sample	Days After Accident	Nonprotein Nitrogen mg.	Total Protein g.	Albumin g.	Globulins g. %			A/G
					α	β	γ	
Case 3	9	163.0	7.03	2.78	2.64	.75	.85	.65
Case 6	10	33.8	5.99	2.99	1.15	.65	1.22	1.00
Controls Avg.—6 males			6.45	3.57	.96	.98	1.06	1.24

SECTION VIII. INDUCED RADIOACTIVITY

A. Interaction of Fast Neutrons and Tissue
B. Interaction of Slow Neutrons and Tissue
1. The (n, p) Reaction
2. The (n, γ) Reaction in Hydrogen
3. The (n, γ) Reaction in Elements Other than Hydrogen
C. Use of Neutron-induced Activity in Calculating Radiation Dose
D. Contribution of Radiation from Induced Tissue Activity to Total-body Dose
E. Unusual Observations Related to Induced Radioactivity
1. The Constancy of the Specific Activity of Serum Sodium
2. The Unexpectedly High Specific Activity of Urine Sodium in Case 3
3. The Inequality of the Specific Activity of Serum and Urine Phosphorus
4. Relative Specific Activities of Serum Sodium and Phosphorus Compared with the Known Neutron Capture Sections of These Elements
F. Summary

VIII. INDUCED RADIOACTIVITY

One of the most interesting and characteristic observations made on this series of patients is the neutron induced radioactivity of their tissues. Besides being a unique observation in itself, the study of the induced activity proved to be of great value in computing the radiation doses. Because of the importance of neutron induced activity, and because the neutron doses accounted for most of the energy dissipated in the bodies of patients, the problem of interaction of neutrons with tissue will be considered briefly. A more thorough discussion of the problem can be found in articles by Zirkle (1947) and Mitchell (1947-a), as well as in any of the recent textbooks on nuclear physics, e.g., Lapp and Andrews, 1948.*

A. *Interaction of Fast Neutrons and Tissue*

When neutrons interact with tissue, several kinds of nuclear reactions take place. Before such reactions occur, however, the fast neutrons are usually slowed down by collisions with atomic nuclei, chiefly with those of hydrogen atoms. The nuclei involved in such collisions are knocked out of molecules and stripped of their orbital electrons. These electrically charged hydrogen nuclei (protons), which recoil at high speeds, produce short but dense ionization tracks in the tissue. The ionization leads to chemical changes in the protoplasm in the manner described in Section IV. This mechanism of energy transfer through ionization by recoil protons accounted for almost half of the total energy dissipated in the bodies of most of these patients.

B. Interaction of Slow Neutrons and Tissue

After a number of collisions the speed of the neutrons is greatly reduced, and they are easily captured by the nuclei of tissue atoms. Atoms differ

* Since these dose calculations were made, additional studies on the interaction of slow neutrons with the body have been published (Tait, 1950; Snyder, 1950).

greatly in their ability to capture slow neutrons and in the nuclear transformations which result. The following three types of nuclear reactions predominate in a tissue subjected to slow neutron bombardment.

1. *The (n, p) Reaction*

Some atomic nuclei (mainly nitrogen in the case of aqueous tissue) give off energetic protons after capturing a neutron. The protons produce tissue damage in the same way as do the recoil protons which result from the collisions between fast neutrons and hydrogen atoms. Ionization from this type of nuclear reaction (called the (n, p) reaction, or neutron-in, proton-out reaction) constituted only about one-quarter of the total ionization which occurred when the body of the patients was bombarded with fast neutrons.

2. *The (n, γ) Reaction in Hydrogen*

Other nuclei emit energetic gamma rays upon capture of neutrons. The (n, γ) or (neutron in, gamma ray out) reaction occurs mainly in tissue hydrogen. Capture by hydrogen is the ultimate fate of the vast majority of neutrons which enter the body. The gamma rays emitted as a consequence of the reaction are very hard (2.2 million electron volts). After emission of the gamma ray, the hydrogen nuclei which have captured neutrons are transformed into deuterium, the heavy stable isotope of hydrogen. Gamma radiation from neutron capture in hydrogen contributes heavily to the total radiation dose of man or large animals irradiated by neutrons. In most of the present cases it accounted for about one-quarter of the total dose.

3. *The (n, γ) Reaction in Elements Other than Hydrogen*

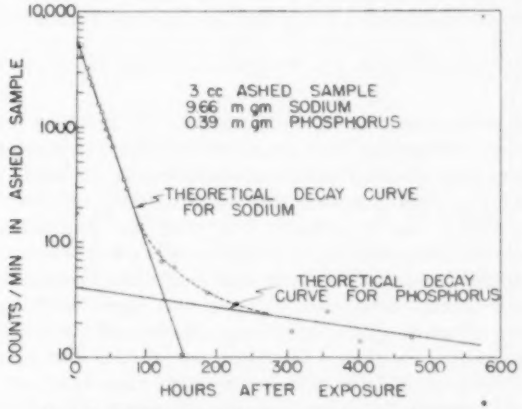
A third class of atomic nuclei becomes radioactive as a result of interaction with neutrons. Chlorine, sodium, phosphorus, potassium and sulfur are the principal elements in tissue which undergo such a reaction with the formation of radioactive isotopes. The intensity of activation decreases in the order of the elements named. The way in which such radioisotopes can be used in computing the neutron dose is discussed below.

All of the above nuclear reactions occur in the body during neutron bombardment, and the chemical changes that take place in the ionized (or excited) atoms are responsible for the ultimate tissue damage.

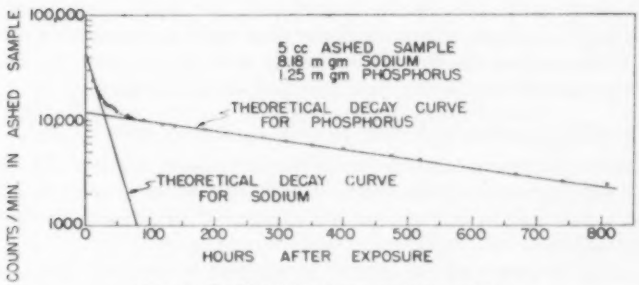
C. *Use of Neutron-induced Activity in Calculating Radiation Dose*

The production of radioactive isotopes in the body is of great practical importance in this study, since measurable radioactivity of the tissue persisted for a considerable period of time after exposure of the body to neutrons. Since the quantitative aspects of this type of nuclear reactions are reasonably well known, the determination of the induced radioactivity provides data from which the number of neutrons that entered the bodies of these patients could be calculated. In these studies only the radioactivity of the serum sodium and phosphorus was determined, and the former was used in the calculation of the neutron doses. Radiochlorine, which decays rapidly (37-minute half-life), was not studied, for practical reasons. The

specific activity, i.e., the ratio of the number of radioactive to stable atoms of sodium and phosphorus in the blood serum and urine of these patients, is given in the composite tables on pages 450 and 451. It should be pointed out that these values are not the only ones that were determined, but they have been selected as being the most valid and representative. The decay curves of representative blood serum and urine samples are given in the



Case 3. **Radioactivity decay curve for blood serum.**



Case 3. **Radioactivity decay curve for urine.**

graphs on page 447. In these graphs, the radioactivity measurements determined experimentally are plotted as points to which the theoretic decay curves of radiosodium and radiophosphorus (indicated by the straight lines) have been fitted.

The assessment of the whole-body dose due to fast neutrons can be made by either of two methods. First, the induced radioactivity can be measured in samples of serum and urine. Second, the total induced radioactivity can be estimated by measurement of the gamma radiation emitted

from the body as a whole at selected distances. In both methods the induced radioactivity is an index of how many slow neutrons existed in the tissue. From these data the total radiation dose can be estimated. The first method is more accurate but requires a more elaborate measuring system. It has been suggested earlier that the specific activity of serum sodium, so determined, be used as an empiric unit of neutron dose in radiation exposures of this type. (See Section II.) The second method employs only a portable gamma-roentgen survey meter and can be carried out quickly.

D. *Contribution of Radiation from Induced Tissue Activity to Total-body Dose*

The radiation dose received by these patients from the induced radioactivity of their tissues has been mentioned briefly. It has been calculated that radiation from the radioactive elements themselves could not have accounted for more than 1 per cent of the total dose received by the body (Hoffman, 1947). It is probably true that the irradiation of tissues adjacent to structures containing large amounts of phosphorus, e.g., bones and teeth, was slightly more intense than that from the radioactivity in the soft tissues, but it is improbable that the dose was significantly raised even in these regions. According to preliminary calculations (Mitchell, 1947), the radioactivity induced in bone adds 8 per cent to the slow neutron dose in this tissue. This would mean an increase of less than 4 per cent in the bones of the present patients. It is certainly true, however, that there was a high radiation level around the gold inlays in the teeth of these patients. This is to be expected since gold atoms are known to have a much larger cross section for the capture of slow neutrons than do most elements in the body. It has been pointed out that a small ulcer was produced in the mouth of case 3, presumably by the radiation given off by a gold filling.

E. *Unusual Observations Related to Induced Radioactivity*

Examination of the data in the tables on induced radioactivity discloses four interesting observations, three of which cannot be explained with certainty in the light of our present knowledge. A discussion of these phenomena follows:

1. *The Constancy of the Specific Activity of Serum Sodium*

The specific activity of the sodium in the blood serum of cases 3 and 4, if corrected for decay, shows relatively little change in the period lasting from 1.2 to 72 hours after the accident. The fall noted in case 6 is probably not reliable, since the late determinations were made on samples which had a counting rate of less than twice background. Thus, equilibrium must have been established quickly between the inert sodium and the radioactive isotope. The lack of change in the specific activity of the serum sodium indicates that this radioisotope could not have been selectively excreted by the kidneys; therefore, it presumably existed in the chemical state normally found in the body. This observed rapid equilibration of radiosodium is

consistent with animal studies of the fate of intravenously injected radiosodium chloride (Manery and Bale, 1941). These investigations show that radiosodium diffuses quickly into most tissues, equilibrium with the normal isotope being established within 20 minutes after injection. In certain other tissues (bone, brain and testes) the penetration of sodium is slower and is not complete for 12 hours. Since radiosodium was produced simultaneously in all sodium compartments of the present series of patients, it is easy to understand how a constant specific activity in serum sodium was established so promptly. The constancy of the specific activity of the serum sodium makes it the logical measurement to use as a basis for neutron dose computations.

In contrast to the rapidly mixing radiosodium, other radioactive elements injected into the body equilibrate more slowly with the stable isotopes in the tissues. For example, radiopotassium does not reach equilibrium with the body potassium until 36 hours after subcutaneous injection (Moore, 1946).

2. The Unexpectedly High Specific Activity of Urine Sodium in Case 3

The specific activity of the sodium was higher in the urine sample of case 3, voided immediately after exposure, than that measured in the serum. This was not the case, however, in the other patients whose urine was similarly studied. This phenomenon cannot be explained in the same way as the increased specific activity of urinary phosphorus, discussed in the next paragraph. It seems likely that the high sodium specific activity in the early urine sample of case 3 was the result of direct neutron irradiation of urine present in the bladder at the time of the accident. The severe reaction of the lower abdomen of case 3 is evidence of the intense irradiation of this part of the body, so it is clear that the bladder urine must have been heavily bombarded by neutrons. This explanation fits the facts of the case, although evidence in favor of it is admittedly circumstantial, for the radioactivity of urine samples passed after the first few hours was not studied.

It should be pointed out that the use of the specific activity of urinary sodium rather than serum sodium in neutron dose computations would not have changed the doses significantly except in case 3, whose dose would have been raised by a factor of 3.4.

3. The Inequality of the Specific Activity of Serum and Urine Phosphorus

The specific activity of phosphorus was higher in the urine than in the blood serum in all cases. In case 3 the specific activity of the urinary phosphorus was 17.9 times higher than that in the serum. In all other cases the radioactivity of urinary phosphorus was easily measurable, while that in the serum was at the background level. A similar disproportion in the specific activity of urinary and serum phosphorus has been observed in neutron irradiated animals (Perley, Langham and Hoffman, unpublished data). The inequality of the specific activity of phosphorus in these two body fluids suggests that the radiophosphorus in the blood existed in a chemical form that was more efficiently excreted by the kidneys than was the major part of the inactive serum phosphorus. The chemical form in which

radiophosphorus exists after nuclear bombardment of tissue is not known, but the reaction discussed below suggests a mechanism by means of which it might be expected to exist in an unusual chemical state.

Atoms which undergo nuclear reactions become dissociated from the molecules of which they form a part. This is known as the Szilard-Chalmers reaction (Lapp and Andrews, 1948). When certain organic molecules are irradiated in the dry state with neutrons a small fraction of the dissociated radioactive atoms is re-incorporated into the molecules in the original positions; thus, neutron bombardment of cystine results in the production of a small quantity of this compound containing radiosulfur in the usual position (Ball, Solomon and Cooper, 1949). In the case of water solutions of phosphorus compounds, an appreciable amount of restitution of the dissociated molecules is not expected. The atoms of elemental radiophosphorus produced in the irradiated tissues as a result of the Szilard-Chalmers reaction can be expected to undergo chemical oxidation with the formation of unknown phosphorus compounds. Some of these radiophosphorus-containing compounds may well be selectively excreted by the kidney.

The rapid selective excretion of radiophosphorus accounts for the low radioactivity of the tissues of cases 1 and 3 at autopsy. Radiosodium had decayed to an insignificant fraction of its initial activity by the time of death of both patients, but physical decay was not responsible for the disappearance

COMPOSITE TABLE OF Na^{24} and P^{32} ACTIVITY IN SERUM

Case	Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm.@ $t = 0$	Na^{24} Corr.* dps.	Na^{24} Corr.* dps./mg. Na	P^{32} cpm./mg. P @$t = 0$	P^{32} Corr.* dps./mg. P
1	Serum I	17.4	—	5	16.8	900	300	18.0	bkg.	—
2	Serum I	17.4	—	5	16.8	56	18	1.1	bkg.	—
3	Serum I	1.2	3.22	3	9.66	6,400	711	73.6	103**	12.8
	II	46.9	3.09	5	15.45	10,240	1,137	73.6	bkg.	—
	III	66.1	3.03	5	15.15	10,700	1,177	77.8	—	—
4	Serum I	1.1	3.20	3	9.60	1,150	128	13.3	bkg.	—
	II	46.8	3.27	5	16.35	2,100	222	13.6	—	—
	III	65.8	3.13	5	15.65	1,800	200	12.8	—	—
6	Serum I	1.9	3.25	3	9.75	620	69	7.1	bkg.	—
	II	46.7	3.16	5	15.80	540	60	3.8***	—	—
7	Serum I	1.8	3.22	3	9.66	260	29	3.0	bkg.	—
8	Serum I	1.5	3.28	3	9.84	180	20	2.03	bkg.	—
9	Serum I	2.0	3.24	3	9.72	135	15	1.52	bkg.	—
10	Serum I	1.4	3.18	3	9.54	110	12.2	1.22	bkg.	—

* Corrected for counter efficiency of 0.15.
** Based on a 3 c.c. sample of serum which had 0.39 mg. phosphorus and 40 cpm. at $t = 0$.
*** Counting rate less than 100% of background.

COMPOSITE TABLE OF P^{32} ACTIVITY IN URINE

Case	Sample	Time Taken (hours after exposure)	mg. P/c.c.	c.c. Plated	mg. P Plated	cpm.@ $t = 0$	P Corr.* dps. @$t = 0$	P Corr.* dps./mg. P
1	Urine I	17.4	—	25	5.3	1,800	600	110
2	Urine I	17.4	—	25	5.3	70	25	4.7
3	Urine I	1.2	—	—	—	11,600	1,290	—
	(Pooled) II**	3.8	—	—	—	3,200	356	—
	III	5.3	0.256	5	1.28	4,120	457	357
4	Urine I	1.2	1.22	5	6.10	2,630	290	47.5
	II	3.1	0.101	5	0.505	310	34.4	68.1
6	Urine I	2.2	0.735	5	3.67	450	50	13.6
7	Urine I	1.2	1.27	5	6.35	170	18.9	2.97
8	Urine I	2.2	1.32	5	6.60	150	16.7	2.53
9	Urine I	1.2	1.12	5	5.60	70	7.8	1.4
10	Urine I	2.2	1.12	5	5.60	70	7.8	1.4

* Corrected for counter efficiency of 0.15.
** Specimens passed at 1.2 and 3.8 hours were pooled.

COMPOSITE TABLE OF NA^{24} ACTIVITY IN URINE

Case	Sample	Time Taken (hours after exposure)	mg. Na/c.c.	c.c. Plated	mg. Na Plated	Na^{24} cpm.@ $t = 0$	Na^{24} Corr.* dps. @$t = 0$	Na^{24} Corr.* dps./mg. Na
1	Urine I	17.4	3.00**	25	75	5,100	1,700	22.5
2	Urine I	17.4	3.00**	25	75	320	102	1.38
3	Urine I	not run						
	II	3.8	1.65	5	8.18	18,300	2,033	248
4	Urine I	1.2	2.94	5	14.7	2,000	222	15.1
6	Urine I	2.2	6.01	5	30.1	2,100	233	7.75
7	Urine I	1.2	1.62	5	8.1	490	43.3	5.35
8	Urine I	2.2	3.32	5	16.6	500	55.6	3.35
9	Urine I	1.2	2.79	5	13.9	240	26.7	1.92
10	Urine I	2.2	2.98	5	14.9	170	18.9	1.27

* Corrected for counter efficiency of 0.15.
** Inert sodium not determined chemically but assumed from tables of normal values.

of radiophosphorus, particularly in case 3, where death occurred within one half-life of the radioisotope. The marked variation in the specific activity of the phosphorus in two body fluids (serum and urine) makes this isotope undesirable for use in neutron dose computations.

4. *Relative Specific Activities of Serum Sodium and Phosphorus Compared with the Known Neutron Capture Cross Sections of These Elements*

The relative specific activity of serum sodium and phosphorus observed in case 3 is not consistent with the physical data concerning their ability to capture slow neutrons. Thus, the capture cross section of sodium for slow neutrons is known to be 90 times that of phosphorus. This means that when sodium and phosphorus are exposed to the same neutron flux in a physical experiment, the radioactivity per milligram of the sodium will be 90 times that of the phosphorus. Instead of following this physical law, the specific activity of serum sodium in case 3 is only 5.6 times as great as that of the serum phosphorus. This single clinical observation is supported by a number of similar findings in animals exposed to neutrons (Perley, Langham and Hoffman, unpublished data). The biologic factors responsible for this finding are not evident unless one supposes a very rapid transfer of radiophosphorus from tissues to the blood stream comparable to that from the blood stream to the urine.

F. *Summary*

Fast neutrons interact with tissue by losing energy through collisions with light nuclei, chiefly hydrogen. The charged recoil protons which result from the collision cause dense ionization and hence tissue damage. When the fast neutrons have been slowed down they are captured by atomic nuclei, and the resultant nuclear reaction may be one of three types: (1) a proton may be given off; (2) a gamma ray may be emitted at the time of the reaction, and (3) a radioactive isotope may be formed, and this decays according to a well known physical law. The first two reactions provide the most important means by which the slow neutrons cause tissue damage in man. The third reaction is important because it provides a transient measure of the number of slow neutrons which entered the bodies of these patients. Four interesting phenomena are discussed: (1) the failure of the specific activity of the serum sodium to decrease during the first few days after exposure; (2) the selective excretion of radiophosphorus by the kidney; (3) the high specific activity of the sodium observed in the urine in case 3 but not in the other cases, and (4) the discrepancy between the measured specific activity and neutron capture cross sections of sodium and phosphorus.

SECTION IX. PATHOLOGY

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B. General Features of the Tissue Reaction
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  2. Cell Damage and Death
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      1. Nonspecific type of nuclear disintegration
      2. Unusual or chromosomal type of nuclear damage
    b. Cytoplasmic changes
      1. Evidence of cytoplasmic dysfunction
      2. Cellular differentiation
  3. Interstitial Tissue Response
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D. Hematopoietic Tissue
E. Reproductive Organs
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IX. PATHOLOGY

The histopathologic observations (although incomplete) have been summarized in the case histories of the fatally injured patients,* and the gross protocols are presented in Appendix I. References to the pathologic changes in radiation injury can be found in the review article by Warren (1942–43), and in the study of the fatally injured Japanese patients (Liebow, Warren and DeCoursey, 1949). The present observations, with few exceptions, conform to or complement the information in the medical literature concerning the effect of radiation on normal tissues in man. This discussion attempts to correlate the pathologic findings with the clinical observations.

A. *Methods*

The postmortem examinations were performed about one hour after death. The examinations were complete in both cases, with the exception of the cranial cavities, the organs of the neck and the hand tissues in case 3. The tissues were fixed in Helly's fluid, absolute alcohol and 10 per cent neutral formalin, and then embedded in celloidin. The sections were stained according to Maximow's hematoxylin-azure II-eosin method.

* A detailed study of the pathologic findings in the present cases will be published in the future.

B. *General Features of the Tissue Reaction*

As a result of the histologic changes observed in these cases, certain general statements can be made about the effects of radiation on normal tissues. These observations are not new but are presented briefly in order to integrate aspects of these cases that have not been discussed up to this time.

1. *Suppression of Mitoses*

The prompt effect of ionizing radiation in suppressing mitotic activity is well known, and the varying rate of recovery of different tissues from this effect also has been established. In general, it appears that the cell types with high mitotic activity (and presumably short life span) show more rapid recovery from this effect of radiation than do the more slowly proliferating, longer-lived cells (Knowlton and Hempelmann, 1949). It is not surprising, therefore, to find that considerable recovery of mitotic activity in many tissues had taken place in the 24 and 10 days between exposure and the time of death in cases 1 and 3. The incidence of cell division in most tissues, although not measured, did not appear to be decreased, except in the epidermis and in the bone marrow of case 3. In fact, the mitotic activity of the lymphoid tissue of case 3 appeared to be even greater than normal. Such delayed "overcompensation" of mitotic activity is well known (Canti and Spear, 1929).

When evaluating the significance of the estimates of proliferative rates in the tissues of these patients, one must consider certain features of the mitotic activity in radiation damaged tissues in particular and in autopsy material in general. In the present cases a great many dividing cells, particularly those in the lymphoid tissues, were in a dying or disintegrating phase, which may be presumed to be more prolonged than the usual brief period of mitosis (presumably 15 to 90 minutes, as in lower animals). Doubling or tripling the mitotic time would increase the number of dividing cells visible at any given time, even though the mitotic activity of the tissue was unchanged. Thus, the incidence of mitoses in these damaged tissues may give a falsely high impression of the rate of proliferation. It should also be stressed that the difference in time elapsing between exposure and death of these patients prevents one from comparing the degree of initial suppression, since more recovery from the early suppression of mitotic activity had taken place in case 1 than in case 3. Finally, it must be remembered, in considering mitotic activity in autopsy material, that some of the dividing cells are able to complete mitosis in the interval between death of the patient and fixation of the tissues. At least, this has been observed in the human epidermis (Thuringer, 1928). Thus, the mitotic activity in both cases, as demonstrated in sections, may be lower than it actually was during life. The conflicting factors just reviewed show the difficulties one encounters in an attempt to interpret quantitatively the influence of radiation on the cell proliferation in this material.

2. Cell Damage and Death

Cell damage which may lead to cell death is obviously the fundamental lesion responsible for the tissue and constitutional reactions observed in irradiated individuals. Tissue regeneration and even the alleged instances of stimulation of cellular activity are secondary to this cell-damaging action of radiation. Cell death is often nonspecific in type, but an unusual type of cytolysis also occurs which, while not unique in radiation injury, is not seen in the commonplace injuries. The nuclear and cytoplasmic aspects of both these types of death are now described.

a. *Nuclear changes*

(1) *Nonspecific type of nuclear disintegration:* The changes in the nuclei of dying cells consist of swelling, hyperchromatosis, pyknosis, karyorrhexis and karyolysis. These changes are indistinguishable, in the usual histologic sections, from nuclear changes seen in other pathologic conditions. Such disintegration is most prominent in the radiosensitive tissues and presumably represents damage or death of the cell during its resting phase.

(2) *Unusual or chromosomal type of nuclear damage:* As discussed in Section IV, cytolysis due to chromosomal change is a common form of death in radiation-injured cells. As expected, these changes are found primarily in the tissues which normally are actively proliferating. The damaged nuclei are greatly swollen and often appear to be "exploding." Fragmentation of chromosomes, bridging between chromosome fragments, and multipolar mitotic figures are conspicuous, as are swelling of the nuclear material and chromosomal remnants in dying or dead cells. As will be brought out later, many of the daughters of these abnormally dividing cells appear to be non-viable. Sometimes nuclear division proceeds without cytoplasmic separation and, as a consequence, double or multilobed nuclei can be observed in a single cell. The mitotic aberrations which can be seen in the photomicrographs of Appendix I were described by Miescher (1925) and are unusually well illustrated in the monograph by Politzer (1934) and in the article by Hamperl (1936). Although this type of nuclear change is the most unusual aspect of radiation-induced cellular injury, it must be emphasized that the reaction does not necessarily represent a specific effect of radiation. Identical changes can be found in the proliferating tissues of patients or animals treated with nitrogen mustards or aminopterin.

b. *Cytoplasmic changes*

(1) *Evidence of cytoplasmic dysfunction:* The changes seen in the cytoplasm of damaged cells, which show either orderly nuclear disintegration or chromosomal abnormalities, are in no way characteristic of radiation injury. Thus, swelling, vacuolation, increased basophilia and other indications of cytoplasmic modification, e.g., waxy degeneration of muscle fibers, can be found as a result of many other types of tissue injury. It was once believed that the increase in size of these injured cells was related solely to the increased intracellular osmotic pressure, but it has since been shown that the swelling cannot be explained by water imbibition alone (Failla, 1940).

That synthesis of protoplasm sometimes continues in damaged cells is shown by the observation that, under certain conditions, irradiated yeast cells may achieve as much as 10 times their normal volume without apparent dilution of their protoplasm (K. Brace, personal communication from R. E. Zirkle). The increased basophilia, particularly conspicuous in tissue lymphocytes, epidermal cells and proliferating connective tissue cells, may well be the result of the accumulation of ribonucleic acid in the cytoplasm (Mitchell, 1942). Sometimes the basophilia is more intense than that seen in actively proliferating, relatively undifferentiated cells, but often it is indistinguishable from that seen in normal stem cells.

(2) *Cellular differentiation:* Recently, in the British literature, emphasis has been placed upon the action of radiation in causing differentiation of anaplastic tumor cells (Glucksmann, 1946). Such an effect, while it may be striking in neoplastic tissue, would of course be difficult to detect in most adult tissues. Thus, although one may consider that the metaplasia of the duct epithelium of the sweat glands represents a similar phenomenon, such a deviation from normal should not be interpreted as true cellular differentiation.

3. *Interstitial Tissue Response*

Most of the connective tissue elements of case 3 showed a striking degree of edema, which was associated with dilatation of blood vessels and lymphatics. In contrast, the interstitial tissues of case 1 showed little edema. The edema in case 3 may have been related, in part, to the circulatory collapse, and therefore might not be the direct response to irradiation alone. Although discrete points of gross and microscopic hemorrhage were evident in case 3, generalized extravasation of erythrocytes into the interstitial tissues did not occur in either case. There was some early hyalinization of collagen fibers, particularly in the regions around the sweat glands and hair follicles in the dermis of the more heavily irradiated regions of the abdomen of case 3.

In contrast to the relatively minor changes in the interstitial tissues of the body, there was widespread necrosis of the connective tissues of the right hand of case 1.

4. *Blood Vessel Changes*

Except in the heavily irradiated hand tissues of case 1, the vascular changes, aside from prominent dilatation, were limited to swelling and occasional death of the endothelial cells in the smaller vessels. There was no endothelial proliferation or thickening and hyalinization of the walls of blood vessels such as has been described as a late effect of chronic irradiation (Wolbach, 1909). Similarly, the adventitial connective tissue changes and loss of collagen in the media described in animals as a consequence of the exposure to radiation in the 30 day median lethal dose range (Bloom, 1948) were not observed.

In contrast to this limited effect on the blood vessels of the body tissues, vascular changes were pronounced in the hands of case 1. These changes,

which were similar in appearance to those found in frostbite and immersion foot, consisted of necrosis of the vessel walls and thrombosis of small and large vessels. It is apparent that most, if not all, of the late gangrene of the hand tissues of case 1 was due to interruption of the blood supply to these tissues.

5. *Cellular Reaction*

a. *Inflammatory cells*

Generalized infiltration of the tissues with leukocytes was not observed except for occasional plasma cells and other unidentified mononuclear cells, presumably of the lymphoid series. In the acutely inflamed tissues of case 1, e.g., the exposed dermis, the cellular reaction was relatively scant and was composed predominantly of mononuclear cells. Polymorphonuclear leukocytes were rare in these regions as well as in the pneumonic patches and beneath the denuded submucosa of the intestines of case 3. This is consistent with the terminal agranulocytosis which occurred in both patients.

b. *Mast cells and their probable relationship to the anticoagulant in the circulating blood*

The occurrence of large numbers of mast cells in almost all of the tissues of case 3 and of a smaller but nevertheless definite increase in number of these cells in the tissues of case 1 is a striking finding which deserves further comment. A similar observation has been reported in the study of the Japanese killed by radiation (Liebow, Warren and DeCoursey, 1949).

Tissue mast cells are not conspicuous in human autopsy material stained by the usual methods, but they can be easily demonstrated in histologic sections of connective tissues stained with metachromatic dyes (Janes and McDonald, 1948). The number of mast cells is increased in tissues which show a chronic inflammatory reaction; they are not increased, however, in acutely inflamed tissues (Janes and McDonald, 1948). Other examples of pathologic states in which mast cells play a conspicuous part are urticaria pigmentosa in man (Lever, 1949) and mast cell tumors in dogs (Bloom, 1942).

The increase in the mast cells is interesting because of its possible association with the anticoagulant demonstrated in the blood of case 3. The intimate relationship between mast cells and heparin was postulated some time ago (Jorpes, 1946) on the basis of experiments which show that the heparin content of tissues parallels the number of mast cells seen in histologic sections (Holmgren and Wilander, 1937; Wilander, 1938). Recent studies in which active heparin has been extracted from mast cell tumors in dogs (Oliver, Bloom and Mangieri, 1947) and from a human scrotum which contained numerous mast cells but no thrombi (Ehrich et al., 1949) may support the contention that tissue mast cells contain heparin. It may be more than coincidence, then, that the mast cell content of the tissues of cases 1 and 3 can be correlated with the presence or absence of a defect in the clotting mechanism of the blood. In case 3, whose blood was uncoagulable at autopsy, there was a great increase in the number of tissue mast cells,

while in case 1, in whom there was no apparent increase in the blood clotting time at death, the mast cells were less numerous. From this observation, as well as from the experimental evidence just reviewed, it seems possible that the anticoagulant in the blood of case 3 was related to, if not derived from, the tissue mast cells.

It should be emphasized again that recent studies show that an increase in circulating anticoagulant cannot be demonstrated in irradiated animals (Cronkite, 1950).

C. *Skin*

The histopathology of acute radiation damage to the skin has been well described and the pertinent literature discussed in a review by Montgomery (1946), as well as in a summary by Warren (1942–43). The acute exudative and ulcerative dermatitis following x-ray, gamma ray or neutron irradiation involves both the epidermis and its appendages and the supporting tissues. As has been pointed out in Section IV, the cellular response in both the epithelium and the dermis becomes manifest only after a latent period of a week or more except when the radiation dose is overwhelming. It is in this respect that radiation "burns" usually differ from thermal burns, in which gross pathologic changes are seen immediately after the injury. The usual type of acute radiation burn produced by a moderately large dose of radiation is characterized by its late development and by multiple, successive waves of ulceration and repair, a process that may continue for many months or years.

Although the radiation received by cases 1 and 3 differed considerably in amount, skin doses of the body in both cases were so large that much cell damage of a prompt character occurred; therefore, it seems reasonable to compare the pathology of the two cases. The histologic picture seen in the skin of the abdomen of case 3, nine days after exposure was characterized by: (a) cessation of mitotic activity in the epidermis and in the hair follicles; (b) necrosis of epithelial cells, with swelling, vacuolation of both the cytoplasm and nuclei, and loss of cellular differentiation, and (c) thinning of the entire epidermis, with a disappearance of the characteristic structural layers. These epithelial changes were accompanied by edema of the underlying dermis and a resultant flattening of papillae, and by the early stage of separation of the epidermis from the dermis. In contrast to the relatively early yet striking and widespread changes of case 3, the skin lesions in case 1, 24 days after exposure, were advanced. Although severe ulcerative and exudate dermatitis was the predominant reaction, regeneration of epidermis and the formation of actual granulation tissue had begun at the edge of burned areas on the abdomen.

In both cases the striking metaplastic changes in the epithelium of the ducts of the sweat glands was the most unusual finding noted in the skin. Metaplasia of this type has not been described previously except for brief mention in an autopsy report of a Japanese in whom the process was be-

lieved to be the result of the thermal burn (Liebow, Warren and DeCoursey, 1949).* Although no dead or disintegrating duct cells were seen in either of the cases under discussion, the metaplastic changes presumably occurred subsequent to destruction of the normal cuboidal epithelium of these ducts. The proliferative changes were in striking contrast to the degenerative phenomena seen in cells of the epidermis. Squamous cell proliferation of the ducts of the sweat glands was much further advanced in case 1 than in case 3, but no normal duct epithelium could be found in either case except in skin taken from lightly irradiated areas. The progressive character of this squamous metaplasia is well illustrated by the way in which it had replaced the original lining and had occluded the lumina of some of the ducts. It is possible that such occlusion of the ducts of the sweat glands may be responsible in part for the cessation of sweat production which has been reported to occur in irradiated skin (Knowlton et al., 1949).

D. *Hematopoietic Tissue*

Study of the histopathology of the radiosensitive hematopoietic tissues of cases 1 and 3 brings out several interesting features:

1. In the first place, in both cases, which differed considerably not only in radiation dose but in the duration of life of the individual after exposure, the lymphoid tissue appeared to be less depleted of cells and more actively regenerating than the bone marrow. This is exemplified by the almost complete aplasia of the bone marrow of case 3 in the face of hypoplastic but proliferating lymphoid tissue. Such a finding might seem paradoxic in view of the fact that lymphocytes are considered to be more radiosensitive than most other blood cells. However, the lymphoid tissue is able to recuperate rapidly, and it must be assumed that the histopathologic picture at the time of autopsy in each case represents recovery rather than absence of injury. This observation suggests that the stem cells in the marrow and lymphoid tissues, which are indistinguishable histologically, actually have different characteristics. Although both types appear to be relatively radioresistant, the stem cells in the lymphoid tissue apparently are somewhat less vulnerable or recuperate more promptly.

2. The proliferation of the lymphoid tissues brings up another interesting point, namely, that the mitotic activity of the lymphoid tissue is not normal with respect to the production of healthy, vigorous daughter cells capable of entering and surviving in the blood stream. Morphologic evidence of the abnormality of cell division is found in the frequent chromosomal aberrations in the medium sized lymphocytes. It is apparent that many dividing cells die in mitosis, and that those which complete mitosis do not form normal-appearing daughter cells. Thus, many of the daughter lymphocytes have large, hyperchromatic and even multiple nuclei, or they have

* Recently, squamous cell hyperplasia and metaplasia have also been observed in the normal mucous glands of the oral cavity of patients receiving radiation therapy (Friedman, M. and Hall, J. W., Radiology **55**: 848, 1950).

formed giant cells. Even the more normal appearing small lymphocytes often have double nuclei or an unusually large amount of basophilic cytoplasm. The failure of the lymphocyte count to rise in the face of proliferation of the parent tissue indicates either that the adult cells were not reaching the blood stream or that they were being destroyed rapidly when once in the circulation.

3. A third interesting point about the response of the hematopoietic tissue is that hyperplasia of the reticulum cells, which has been previously reported (Liebow, Warren and DeCoursey, 1949), was not observed in these cases. The radio-resistant reticulum cells became more prominent in the lymphoid tissue and bone marrow because of depletion of the leukocytes, but hyperplasia of the reticulum was not evident. This is in contrast to observations in the Japanese, which showed that reticulum hyperplasia was the usual finding in the patients dying seven to 10 days after exposure. It had even begun in the bone marrow of a few patients dying six days after exposure.

In addition to the findings just noted, two other facts stand out about the bone marrow response in cases 1 and 3. First, the apparent damage to the reticulum cells in the irradiated vertebral bone marrow of case 3 suggests that the radiation dose in this tissue was high, since the radio-resistance of this type of cell is well established. This is in conflict with the concept that most of the radiation was absorbed in the superficial layers of the anterior surface of the body of this patient. (See Sections II and X.) Second, the large number of cells dying during mitosis in the marrow of case 1 is an unexpected finding so long after exposure.

E. *Reproductive Organs*

The lesions in the reproductive organs are identical with those described in human subjects many years ago (Schinz and Slotopolsky, 1928), and with the well known testicular abnormalities in experimental animals, first described in 1903 (Albers-Schönberg). Sections of the testes of the two fatal cases clearly illustrate the sequence of events that takes place in germinal tissue exposed to an overwhelming dose of radiation. It is irrelevant that the radiation dose differed in the two cases because, in both instances, it was undoubtedly much higher than that necessary to produce permanent sterility.

In case 3, a few poorly preserved and highly abnormal spermatocytes and even a few spermatogonia were observed among the clumped necrotic cells and debris within the lumina of the seminiferous tubules. In contrast, there was little evidence of cellular debris in case 1, although a few swollen, degenerating germinal cells were seen. The lining cells of the tubules in the latter case consisted wholly of abnormally large Sertoli cells. In addition, there was hyalinization of the basement membrane, an indication of involution and atrophy of this organ. The sequence of events in these cases is in accordance with the histologic pattern noted in the Japanese. Sloughing and disintegration of the epithelium were evident in a Japanese patient dying four days after exposure. In other patients the destruction of germinal epi-

thelium continued well beyond the second week. In contrast to the tubular atrophy, the interstitial tissue in the Japanese appeared normal or hyperplastic.

Even though the testicular changes can be explained by the direct damaging action of radiation, indirect factors must be considered also, since these tissues are known to be very sensitive to many diverse and generalized body changes, such as malnutrition and acute or chronic infectious processes. It is highly unlikely, however, that such systemic factors played a primary rôle in the pathogenesis of the lesions noted in the testes of cases 1 and 3, although they may have contributed to the overall picture seen at autopsy.

The prolonged effect of radiation on the spermatogenic cells is shown by the sperm counts and biopsies in case 4. Why regeneration should be so markedly delayed in this tissue is not clear. Such a delay is in marked contrast to the other radiosensitive, actively proliferating tissues, such as the lymphoid tissue, bone marrow and intestinal epithelium, which show prompt recovery (Liebow, Warren and DeCoursey, 1949).

F. *Gastrointestinal Tract*

The loss of the sections of most of the alimentary tract of case 1 prevents a comparison of the histologic appearance of the intestine in the two fatally injured patients. However, it can be said from the examination of the gross specimens that the most intense reaction in case 3 occurred in the jejunum and ileum, while that in case 1 occurred in the colon. This observation in case 1 is in keeping with the findings in the Japanese dying after the second week. In these persons the large bowel was also the site of the most severe damage. It is interesting that the ulcer in the colon was located at the site of a previously healed inflammatory reaction.

The essential lesion in case 3, however, was the almost complete loss of intestinal epithelium, particularly in the small intestine; there were also mononuclear cell infiltration, edema and hyperemia of the submucosal tissues. The few remaining epithelial cells were found mostly in the intestinal crypts, and they appeared to be severely damaged. The most obvious abnormalities were the marked enlargement of the cells and the chromosomal aberrations. In a few portions of the jejunum and ileum, the ulceration had extended beneath the epithelium into the underlying submucosal tissue. It is possible that some of these ulcerations may have occurred in disintegrated Peyer's patches. Myriads of bacteria were present on the denuded surface of the gut, but there was little bacterial invasion of the underlying tissue. This delay in the invasion of the intestinal wall by bacteria, even in the absence of a cellular reaction, has been observed in irradiated animals (Warren and Whipple, 1923).

In contrast to the almost complete destruction of intestinal epithelium in case 3, the gastric mucosa showed relatively little damage. This is consistent with the observations in the injured Japanese patients.

G. *Heart*

Except for a spotty endocardial thickening in the heart of case 1 and the petechial hemorrhages in case 3, there were no significant lesions of the valves, the endocardium or the myocardium in either case. The hemorrhagic fibrinous pericarditis of case 1 appeared to be acute in some places and subacute in others. In the latter regions, early organization of the fibrinous exudate was seen. The process thus appeared to be at least a week to 10 days old, and must have started about the time of the friction rub which followed the tachycardia on the fifteenth postexposure day. Except for the absence of bacteria and cellular reaction, there was nothing specific about the appearance of this pericardial reaction. Pericarditis of this nature has not been reported previously in patients with thermal or radiation injuries or in patients with Wolff-Parkinson-White syndrome. The cause of the pericarditis, therefore, is not apparent, although infection cannot be excluded, in the absence of blood cultures, even though organisms could not be seen in sections stained with bacterial stains.

H. *Adrenal Glands*

Since certain of the clinical and metabolic responses of these patients were assumed to be dependent upon adrenal cortical dysfunction, the study of the adrenal glands becomes of great interest. It is surprising that the adrenal cortex of case 1 showed only slight morphologic changes, particularly in view of the very high excretion level of the corticoid-like substances. In contrast, the adrenal cortex of case 3 showed evidence of distinct damage, characterized by vacuolation and necrosis of cortical cells in both the zona glomerulosa and the zona fasciculata, and edema of the cords. Reference has been made to the similarity of this reaction and the "tubular degeneration" of the adrenal cortex observed in patients dying in a state of cardiovascular collapse resulting from overwhelming infection (Rich, 1944).

It is appropriate to consider the rôle of the adrenal glands in the acute radiation syndrome at this time. This subject has been reviewed recently (Selle, 1949), and there seems to be little doubt that adrenal dysfunction is responsible for some of the clinical response in irradiated animals. Evidence for disturbance in the adrenal function comes from investigation of the postmortem histologic changes in the glands of irradiated human beings and animals and from studies of the cholesterol content of the glands in rats. Thus, the Japanese, dying of radiation injury, showed adrenal atrophy; similarly, studies of the histology of the heavily irradiated adrenal glands of rabbits have shown evidence of cell damage (Engelstad and Torgerson, 1937). Recent observations on the organ weight and cholesterol content, as mentioned above (Patt et al., 1947), attest to the hyperactive state of the adrenal gland in animals exposed to doses of x-rays in the median lethal range. In the terminal stage of the illness of fatally injured animals, the adrenal activity, as indicated by cholesterol content, may decline. This is in

keeping with the concept of the exhaustion stage of the *general adaptation syndrome*. Hypophysectomy, or the previous injection of adrenal cortical extract in rats, wipes out the adrenal cholesterol response (Patt et al., 1948-b).

Although it has been reported that pretreatment with desoxycorticosterone protects mice against lethal doses of x-rays (Ellinger, 1947), recent experiments do not confirm this observation (Straube et al., 1949). It has been observed that the mortality rate for irradiated normal and adrenalectomized mice maintained on a salt diet is the same, even though the mean survival time for the intact animals is somewhat longer (Straube et al., 1949). Similar experiments in other laboratories, however, indicate that adrenalectomized mice are more susceptible to the lethal action of ionizing radiation than normal mice (Cronkite, personal communication). Thus, it is apparent that the rôle of the adrenal gland and its hormones in causing radiation death is not clearly understood at the present time; it is certain, however, that the adrenal glands play a conspicuous part in shaping the clinical response of the animal to irradiation.

I. *Liver*

There was no microscopic evidence of liver damage in case 1. In case 3, however, occasional dead liver cells were seen, and there was edema of the cords. The changes in the latter case are compatible with the clinical evidence of frank liver insufficiency. Although the liver parenchyma is said to be highly radio-resistant, evidence of liver damage has been described in animals which have received large doses of radiation in the region of the abdomen (Pohle and Bunting, 1932; Warren, 1942). It has been stated recently that the histologic changes seen in the liver of animals subjected to lethal doses of total-body radiation (not exceeding 1,200 roentgens or its equivalent) are probably secondary to damage elsewhere in the body (Bloom, 1948). In case 3, however, the heavy irradiation of the abdomen may have resulted in direct damage to this organ, in addition to the indirect or secondary reaction of the liver to injury of the body as a whole.

J. *Kidneys*

Aside from the infarct in case 1, the only kidney lesion of significance was the moderate degenerative change noted in cells high in the tubular system of case 3. This lesion, together with the extrarenal shunt (Trueta et al., 1947), was probably responsible for the terminal anuria and nitrogen retention noted in this patient. In view of the widespread tissue breakdown, one might wonder if the kidney lesion described in this patient is similar in nature to that seen in the *crush syndrome*. Actually, the tubular damage in this case is quite different from the lower nephron syndrome seen in traumatic shock. The kidney changes after traumatic shock usually occur lower in the tubules, are focal in nature, and are often associated with precipitation of blood pigments within the tubules (Mallory, 1947).

K. *Summary*

Cell injury or death in all radiosensitive organs and in the heavily irradiated superficial tissues was the fundamental histologic lesion noted in cases 1 and 3. Often there was nothing distinctive about the type of cellular damage and disintegration, but cell death during or shortly after mitosis was conspicuous, particularly in the actively proliferating tissues. Such cytolysis resulting from chromosomal damage is characteristic of but not unique in radiation-damaged tissues, for it is also noted after injury by nitrogen mustards and other mitotic poisons. In contrast to the widespread destructive processes, proliferative changes were noted only in the ductal epithelium of the sweat glands, even in the heavily irradiated regions of the skin of both cases.

There was a widespread inflammatory reaction noted in both cases due to infection and other factors (aspiration pneumonia, infarction of the kidneys, etc.). The cellular exudate in the inflamed regions was unusual, in that neutrophils were rare. There was a marked increase in the number of mast cells in case 3, and a slight increase in cells of this type in case 1. The generalized mast cell infiltration of the tissues of case 3 and the uncoagulability of his blood at death may be more than a chance association.

Certain pathologic changes in individual organ systems are believed to be the result of direct radiation damage plus a secondary reaction to tissue destruction or organ dysfunction elsewhere in the body. Thus, the liver damage of case 3 is probably a result of primary and secondary cell injury. Also, the "tubular" degeneration of the adrenals of case 3 is similar in appearance to that described in patients with overwhelming infections. The changes in cells high in the tubular system of the kidneys of case 3 resemble those seen in cases of dehydration more closely than the lower nephron syndrome described in patients with traumatic injuries. There is no obvious explanation for the serofibrinous pericarditis of case 1, although infection is a possibility which cannot be excluded.

SECTION X. RECONSIDERATION OF THE CALCULATED RADIATION DOSES IN TERMS OF THE OBSERVED BIOLOGIC RESPONSE OF THE PATIENTS

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X. RECONSIDERATION OF THE CALCULATED RADIATION DOSES IN TERMS OF THE OBSERVED BIOLOGIC RESPONSE OF THE PATIENTS

The discussion of the radiation doses in Section II was intentionally limited, insofar as was possible, to the physical problem, and consideration of biologic variables was kept to a minimum. Now that the clinical and pathologic response of the patients has been presented, it is desirable to review the radiation doses emphasizing the biologic aspects. Therefore, the reliability of the dose computations will be re-assessed; those characteristics of the radiation which may be expected to influence the clinical response will be re-evaluated, and, finally, specific tissue reactions will be compared quantitatively with those produced by known amounts of x-rays or gamma rays. Such a correlation of physical and biologic data is of great importance because of the scarcity of accurate information about radiation doses in human subjects with acute radiation injury.

A. *Reliability of Radiation Dose Calculations*

The uncertainties in the computation of radiation doses in these patients were stressed in Section II. It seems appropriate to reëxamine the postulates on which the calculations were based. In this way, the reliability of the doses can be assessed and an idea of the direction of possible error may be gained in some instances.

1. *Doses in Terms of Energy Units*

Consider for the moment the radiation dose in terms of energy dissipated in the body (table 1, Section II). It has been pointed out that the validity of these computations rests on the basic assumption that the incident neutron flux can be calculated from the specific activity of the serum sodium. The

introduction of biologic variables in the form of possible differential handling of radiosodium by the body poses a problem not implicit in calculations based on the physical interaction between neutrons and sodium. However, the simultaneous in vivo production of radiosodium by neutrons in all body sodium compartments, and the known ability of radiosodium to reach a prompt equilibrium with body sodium, argue against errors due to biologic factors. This view is substantiated by the constancy of the sodium specific activity, which provides, in itself, strong experimental evidence against selective handling of the radioisotope by the body. Taking these facts into consideration, the use of sodium specific activity for the determination of neutron flux appears to be sound on both theoretic and experimental grounds.

Assuming that the basis used for neutron dose calculations is valid, the major sources of error in the dose calculations are the lack of good experimental data about incident neutron energy and the possibility of improper interpretation of the nuclear reactions. In considering the first of these sources of error, it should be pointed out that the arbitrary value for average neutron energy was chosen so that the errors in dose are likely to be high rather than low. This means, therefore, that the total energy dissipated in the body may be less than that indicated in table 1. Corrections for the use of unduly high neutron energies would result in an increase in the surface doses even though the total-body doses would be diminished. The second of these possible errors, that due to misinterpretation of nuclear reactions, deals with unknown factors which must await further experimentation for clarification.

In evaluating the gamma ray component of the radiation doses, it should be realized that considerable experimentation was undertaken to determine the self-dosage of the body by the captured gamma rays (column 2 in table 1). A mock-up of the body containing radiosodium was utilized in these studies and the reciprocity theorem was employed (Hoffman, 1947). It seems reasonable to accept with confidence these doses and the prompt primary gamma doses as being in the proper range. In contrast to these doses, the delayed gamma ray dose (column 4, table 1) depends upon an estimate of how long the operator remained in a region of known gamma ray intensity. It is conceivable that this dose estimate, particularly in case 1, may be inaccurate.

2. *Doses in Terms of Roentgen-ray Equivalent*

The possible errors encountered in converting energy dissipated in the body into x-ray equivalent doses have been emphasized so strongly that little need be added here. It should be pointed out again that the overall R.B.E. used for the neutrons in these calculations may well be low for selected effects in specific tissues. Thus, the effective dose in such tissues as the gonads and lens, organs known to be highly sensitive to repeated neutron exposure, might well be higher for an acute exposure than that indicated in table 2. The difference between the actual depth dose curves for neutrons of this energy and for 80-kv x-rays also should be stressed once more. Tissue

ionization caused by irradiation with neutrons of this energy does not fall off so rapidly below the skin surface as does that produced by soft x-rays. Thus, for a given amount of energy dissipated in the body, the skin dose, in the case of the neutrons, would be less than that for x-rays.

B. *Reconsideration of the Characteristics of the Radiations and Their Biologic Implications*

Now that the validity of the computed doses has been discussed, it is fitting to reconsider the unusual characteristics of the radiations which might influence the clinical response of the patients. Although much of this information has been stated before, the biologic implications of these radiation characteristics will be reiterated and summarized.

1. *Uneven Distribution of the Radiation in Cases 1, 3 and 4*

It has been pointed out repeatedly that the doses quoted in table 1 represent the *average* dose of radiation distributed evenly over the entire body of the individual. In those cases where the incident radiation was nonuniform, the value for the average dose cannot be taken literally for any part of the body. Thus, the abdomens of cases 1 and 3 and the head and left arm of case 4 received a greater amount of radiation than that designated by the average dose. The heavy irradiation of these parts of the body must be kept in mind when the reactions of the abdominal skin, the intestines and the superficially placed hematopoietic tissues of cases 1 and 3 are studied and when the epilation of case 4 is considered.

2. *Depth Dose of the Radiation*

The limited power of penetration of moderately fast neutrons in aqueous tissue has been stressed, and the difference in the shape of the depth dose curves for neutrons of this energy and for 80-kv x-rays has been pointed out. The distribution of the radiation dose in the body is important in determining the response of the individual. Preliminary reports of a current investigation indicate that, in swine, the same dose of 200-kv x-rays is more injurious if given half to one side of the body and half to the opposite side than if the entire dose is administered to one side (J. L. Tullis, personal communication). In the case of the more heavily irradiated survivors of these radiation accidents, the superficial nature of the body dose undoubtedly accounts for the fact that the patients did not show more serious constitutional reactions. This is somewhat analogous to animal experiments, which show that protection of part of the hematopoietic tissue increases the median lethal dose and diminishes the damage to the formed elements of the blood (Jacobson et al., 1949-b).

It should be emphasized again that the superficial radiation dose due to beta rays and secondary x-rays was not taken into consideration except in the case of the hands. Such radiations also may have contributed to the damage of the exposed skin of the face, particularly in the patients nearest the assembly. Furthermore, the dose calculations do not take into account scattered slow neutrons of thermal energy. Slow neutrons would have con-

tributed to the induced radioactivity in the body tissues, but would produce maximal tissue ionization only 0.3 cm. below the surface (Capron, Faes and Tavernier, 1949). The unknown amounts of such soft radiations, i.e., beta rays, soft x-rays and thermal neutrons, would have enhanced the skin effects without having much influence on the systemic response of the patients.

The sharp localization of the epilation of case 4 and the partial shielding of the lens of his right eye by the bridge of the nose are a consequence of the soft quality of much of the incident radiation.

3. *Dose Rate of the Incident Radiation*

It is well known that the biologic effect of radiation depends to some extent upon the dose rate. For the range of dose rates often used in biologic experimentation, it has been shown that decreasing the dose rate lessens the biologic effect. Perhaps it is not valid, then, to compare the clinical reactions produced by radiation delivered at a rate of thousands of roentgen equivalents per minute with the response of patients and experimental animals irradiated by radiation from x-ray tubes, the usual output of which is about 50 roentgens per minute.

The effect of dose rate on biologic reactions has been reviewed in a symposium (Gray, 1944; Ellis, 1944). This symposium considers the results of irradiating various biologic materials at vastly different dose rates, ranging from very low radiation intensities to 40,000,000 roentgens per minute. The data indicate that the quantitative biologic effects of radiation are dependent on dose rate at low intensities but not at high intensities. The rate above which the biologic effects become dose-rate-independent is 5 to 10 roentgens per minute for most animal reactions. In contrast, the reactions of some plants (algae) show dose-rate-dependence up to intensities of 1,000 to 2,000 roentgens per minute. Although it has been reported that the response of human skin is dose-rate-dependent at intensities up to 500 roentgens per minute, this has not been confirmed by recent investigation (Ellis, 1944; Schottelndreyer, 1949).

The evidence just reviewed suggests that the very high dose rate responsible for the injury of the present cases should not be expected to have been inordinately effective in modifying the clinical responses of these patients.

4. *Specific Effects of Neutron Irradiation*

The variability in the biologic effectiveness of neutrons as compared with other radiations was mentioned in Section IV. Studies of the response of skin to neutron and x-ray irradiation provide an example of the inconstancy of the R.B.E. for *different* effects in the *same* tissue (Stone, 1948). Thus, although one rep of neutrons delivered in a single dose is equivalent to 2.5 reps of x-rays in producing erythema, it is equal in effectiveness to 4 reps of x-rays in causing epidermolysis and late skin changes. An example of the variation in the R.B.E. of neutrons and x-rays for the *same* effect in *different* tissues is found in an experiment in which the effects of localized acute irradiation of rabbit testes were studied (Lampe and Hodge, 1943). When compared to x-rays, fast neutrons are relatively more damaging to the

germinal epithelium than to skin. This is shown by the fact that sterilization was produced by neutron irradiation in the absence of permanent injury to the overlying skin, whereas, in the case of x-rays similarly applied, a comparable testicular effect was achieved only by doses which caused lasting skin damage.

Besides the variations just mentioned for acute irradiation, it has been found that the R.B.E. of neutrons is dependent on the dose rate. When the lethal effect in mice of neutrons and x-rays is investigated at different radiation intensities, it is found that the effectiveness of neutrons as compared to x-rays or gamma rays is much greater for chronic than for acute exposures (Henshaw, Riley and Stapleton, 1947; Mitchell, 1947; Evans, 1949). Similarly, the selective damaging action of neutrons in specific tissues is exaggerated when exposures are protracted. Thus, chronic neutron irradiation of mice causes more damage to the gonads and lens than to other tissues (Evans, 1948). No studies have been done on the R.B.E. of neutrons and x-rays or gamma rays at high intensities. If one extrapolates the dose rate data just mentioned to the present situation, one would expect the R.B.E. to be relatively low.

This discussion of the specific effect of neutrons emphasizes the difficulties encountered in choosing a single value for the R.B.E. for use in neutron dose calculation. The evidence just presented, however, suggests the best approximation of the R.B.E. for the overall response of the individual can be made by using a relatively low value. Since the range of the R.B.E. in acute biologic responses is from 4 to 10, the factor of 5 used in the present computations seems reasonable.

C. *Consideration of the Quantitative Aspects of Selected Tissue Response*

It is appropriate to conclude this section by considering specific tissue reactions in man; also, the dose estimates in the present cases will be compared with the x-ray doses known to produce comparable tissue responses. Except for the estimates of lethal doses, most of the clinical data presented below were obtained from studies using local rather than total-body irradiation.

1. *Lethal Doses of Total-Body Radiation in Man*

The median lethal dose of radiation is not known with accuracy for man, but it may be assumed to be about 400 ± 100 roentgens of gamma rays.* The mixed x-ray equivalent doses listed in table 2 (Section II) obviously cannot be compared with this value because of differences in the type of radiations and the unusual exposure conditions. If one ignores the important consideration of the depth distribution of tissue ionization and converts megagram-roentgen dose directly into its gamma ray equivalent (using an R.B.E. of 5), the radiation doses turn out to be 290 roentgens for case 1, 880 roentgens for case 3 and 180 roentgens for case 4. Although such an

* This figure is based on the opinion of a group of 24 experts in radiology and radiobiology (R. R. Newell, personal communication).

interpretation of the data is not strictly acceptable, the computation suggests that, in terms of energy loss in the body, the present doses in the fatally injured patients are of the same order of magnitude as that which has been estimated to be lethal in man.

2. *Epilation*

There is considerable individual variation, particularly with age, in radiation-induced epilation of the scalp in man. Therefore, it is difficult to express the minimal epilation dose as a single value. However, the dose of soft x-rays recommended for temporary therapeutic epilation in the treatment of ringworm of the scalp is not less than 300 roentgens of soft unfiltered x-rays (MacKee and Cipollaro, 1946). Recently it has been stated that complete temporary epilation is not achieved except by administering 75-kv unfiltered x-rays in such a way that the minimal and maximal doses in a given field lie between 375 and 500 roentgens (Pendergrass and Mahoney, 1948). Thus, it appears that the calculated dose of the soft x-ray equivalent for case 4 approximates the x-ray dose known to produce comparable clinical effects.

3. *Sterilization*

The doses of radiation which cause temporary or permanent sterilization in the male are not known with certainty (Dunlap, 1947). However, it has been stated that 250 roentgens of x-rays (energy undesignated) will cause temporary but not permanent sterility (Ellinger, 1941; Glucksmann, 1947). The response of the germinal tissues noted in case 4, then, is not unexpected in view of the calculated radiation doses. The fact that irreversible damage did not occur suggests that, unlike chronic exposure, acute neutron irradiation in these cases was not inordinately effective in damaging germinal tissue. As has been pointed out, however, animal experiments suggest that neutrons delivered as a single dose are more damaging to germinal epithelium than are doses of x-rays which produce comparable skin effects (Lampe and Hodge, 1943). Thus, it is likely that the effective dose of the gonads in the patients under discussion was greater than that indicated in the dose tables.

It should also be pointed out that the partial shielding of case 4 may have caused the gonadal dose to be lower than the average body dose.

4. *Delayed Damage to the Lens of the Eye*

The dose of x-rays required to produce cataracts in animals varies directly with age (Warren, 1943). The minimal cataractogenic dose of x-rays in adult humans is not known, but it has been reported that 875 roentgens of 130-kv x-rays and 1,000 roentgens of gamma rays caused cataracts in patients treated for cancer of the eyelid (Hunt, 1947). The radiation dose of the 10 Japanese who developed radiation cataracts is not known exactly, but an idea of its order of magnitude is gained from the fact that all showed epilation (Cogan, Martin and Kimura, 1949). The cataractogenic properties of acute exposure to neutrons have not been studied, but it seems clear that repeated neutron exposure is more damaging to the

lens than to most other tissues. The early development of the cataract in the left eye of case 4 is not unexpected in view of the fact that his head probably received more radiation than that indicated by the average body dose.

5. *Initial Reaction or Radiation Sickness*

This response is so variable that it is not worth serious consideration as an index of the radiation dose. Nevertheless, it has been shown that 100 roentgens of 200-kv x-rays can be delivered to the entire body of a patient without causing symptoms of any sort (Cantril et al., 1947). If the important factor of the distribution of tissue ionization in the body is ignored and the megagram-roentgen dose of case 6 is converted into its gamma ray equivalent, a value of 86 roentgens is obtained. As has been pointed out, the significance of such a dose conversion is limited, but it does suggest that total-body radiation approximating 100 roentgens or less (as was received by cases 6 and 7) need not cause symptoms of radiation sickness.

6. *Bone Marrow Damage*

Experimental studies in animals and clinical experience in man indicate that the blood forming tissues are exceedingly radiosensitive. In man, the lymphoid tissue is considered to be of the same order of radiosensitivity as the erythroblastic tissue of the bone marrow (Bloom and Bloom, 1947). Histologically, the damage in the marrow and lymphoid tissues in several species of animals produced by whole-body irradiation with either gamma rays or fast neutrons in equivalent doses is identical (Bloom, 1947). For this reason, the marked damage of the deeply placed vertebral marrow of case 3, which is out of proportion to the lymphatic tissue reaction, represents a distinctly unexpected finding. This observation cannot be explained on the basis of enhanced scattering of neutrons by the relatively heavy bone tissue, with the resultant increased energy dissipation in the bone and adjacent tissues such as is known to occur with soft x-rays (Spier, 1946). The well known neutron scattering properties of calcium and phosphorus indicate that the energy absorption in bone is not increased over that in soft tissues. Nor can severe marrow effects be explained by induced radioactivity in bone phosphorus, which would have accounted for only a small percentage of the total ionization in the bony tissue.

Hence, one cannot interpret the marrow damage of case 3 on the basis of any known phenomenon occurring as a result of the interaction of neutrons and bone. The extreme damage, even to the radio-resistant reticulum cells of the deep-seated vertebral marrow of case 3, is difficult to reconcile with the present concept of depth dose of the incident radiation as presented in Section II.

D. *Summary*

After considering the tenets on which the radiation dose computations are based, it is concluded that the use of the specific activity of the serum sodium for calculating the neutron flux is justifiable. The values assumed for the

average energy of the incident neutrons are such that errors in the neutron dose are believed to be on the high side. Reconsideration of the characteristics of the incident radiations suggests that insofar as the quantitative aspects of the biologic reactions are concerned, there was no reason to expect unusual clinical responses in the present cases. When specific tissue reactions of the present cases are considered, it is noted that they are in agreement with those produced by comparable x-ray doses, with one exception—the severe damage to the vertebral bone marrow of case 3.

ACKNOWLEDGMENTS

The clinical study reported in this paper is the result of the cooperative efforts of many persons in several laboratories and hospitals. The individual contributors are too numerous to mention, but the following gives credit to the persons in charge of various phases of the study.

Care of the Patients

Dr. L. H. Hempelmann and Dr. Alfred M. Large took care of the patients involved in the first accident. Dr. Jack Brooks, Dr. John DePersio, Dr. Hugh Dwyer and other members of the medical and nursing staff of the Los Alamos Hospital gave professional assistance. Dr. Robert S. Stone, then Director of the Health Division at the Metallurgical Laboratory of the University of Chicago, spent several days with the patients shortly after the first accident and gave valuable advice by telephone during the later stage of the illness of the first patient.

Dr. Paul O. Hagemann and Dr. A. M. Large attended the patients exposed in the second accident. Dr. J. G. Allen, Dr. C. Beller, Dr. J. Brooks, Dr. L. H. Hempelmann, Dr. J. J. Nickson, Dr. J. F. Nolan, Dr. C. Prosser, Dr. H. O. Whipple and the members of the professional staff of the Los Alamos Hospital saw the patients in consultation. Dr. Stafford L. Warren, then of the Manhattan District, also examined these patients soon after the accident.

Pathology

Dr. Hermann Lisco conducted the pathologic studies. He was assisted by Dr. Frank Inda in part of the study. Some of the biopsy specimens were studied by Dr. Charles Eckert, of Washington University in St. Louis.

Hematology

Miss Annamae Dickie and her co-workers did the hematologic studies before and after both accidents. Detailed cytologic studies of the fixed blood cells were made by Dr. L. H. Hempelmann and Dr. Norman P. Knowlton. Dr. Carl V. Moore, of Washington University School of Medicine, St. Louis, studied the fixed blood smears of the patients and examined some supravital blood samples and bone marrow preparations. Blood clotting studies on the patients injured in the second accident were made by Dr. J. Garrott Allen.

Routine Blood Chemistry

The chemical determinations on the blood specimens taken at the time of the accidents were made in the laboratory of the Bruns General Hospital of the United States Army. Most of the late chemical studies were carried out at the laboratory of the Los Alamos Hospital.

Special Chemistry of the Blood and Excreta

Samples of blood and excreta were sent to the Metallurgical Laboratory for investigation of certain chemical changes. The electrophoretic patterns of the plasma proteins were determined by Dr. E. S. G. Barron; the urinary amino acids were studied by Miss E. Katz, and the quantitative analysis of urinary porphyrins, urobilinogen and corticoid-like materials was made by Dr. S. S. Schwartz and his collaborators.

Radiation Physics

The physical measurements of the critical assemblies were made by Dr. Paul Aebersold, Dr. J. G. Hoffman and members of the Physics Divisions of the Los Alamos Laboratory. The induced radioactivity of blood and urine samples was determined by Mr. Don Duffy, Dr. Wright Langham and Miss Ann Perley. The calculations and experimental work

required to determine the radiation doses were performed by Dr. Joseph G. Hoffman, with the help of Dr. Carson Mark, Dr. Philip Morrison, Dr. H. O. Whipple and Dr. T. N. White. Dr. G. Failla made valuable suggestions about the way in which to express radiation doses.

Photography and Graphs

The color photographs were taken by Mr. John Michnovicz. The photomicrographs were taken by Dr. Lisco and Miss Katheryn Haley. The graphs were drawn by Mr. L. F. Jacot and Mr. J. G. Russell.

Follow-up Medical Examinations

Examinations subsequent to the accident were carried out by Dr. Loren Blaney, Dr. L. H. Hempelmann, Dr. Norman P. Knowlton and Dr. H. O. Whipple.

Writing of the Report

The original intent of the authors was to present a complete clinical and pathologic study of these patients. Because of circumstances which prevented one of the authors from participating in the final preparation of the manuscript, it was decided to emphasize the clinical aspect of the report and to include as much of the pathologic studies as was available. The compilation of the manuscript was accomplished with the help of many persons, including Dr. J. C. Aub, Dr. H. A. Blair, Dr. A. M. Brues, Dr. O. Cope, Dr. J. Dealy, Dr. L. L. Engel, Dr. G. Failla, Dr. H. L. Hardy, Dr. J. W. Howland, Dr. L. O. Jacobson, Dr. T. R. Noonan, Dr. S. Warren, and Dr. R. E. Zirkle, all of whom read parts of the early manuscripts. The facilities of the Huntington Memorial Hospital in Boston were made available for the writing of the report, which was financed largely with funds from the Atomic Energy Commission. The final manuscript was prepared by the senior author, with the assistance of Miss Shiela Carr and Dr. James Dealy. Mrs. Lynn Anderson and Mrs. Helen Emerson also gave valuable help in completing the report. As a result of the untiring efforts of Dr. Ralph Carlisle Smith, Mr. Loris Gardner and their associates, a limited number of copies of the report was reproduced in March 17, 1950, by the Los Alamos Scientific Laboratory as a three volume document (LA-1095, LA-1096 and LA-1097). The present report is a revised version of the Los Alamos document.

It should be emphasized that the opinions expressed in the report are mainly those of the senior author and do not necessarily represent the concepts of all of the collaborators.

Appendix

I. A. Gross Protocol and Selected Photomicrographs (Case 1)
B. Gross Protocol and Selected Photomicrographs (Case 3)
II. Statistical Analyses of the Blood Counts
A. Leukocytes
B. Erythrocytes
III. Response of the Neutrophils and Lymphocytes
A. Neutrophils
B. Lymphocytes

Appendix I

A. Gross Protocol and Selected Photomicrographs

Case 1

External Appearance

The body is that of a well developed, obese, sthenic young male individual, said to be 25 years of age and measuring 178 cm. in length. The estimated weight is 85 to 95 kg.

The body is still warm. Beginning rigor mortis is found in the neck, the jaws and somewhat in both elbows; it is absent in the legs. There is considerable hypostasis of blood in the dependent parts of the body and a slight pitting edema is noted around both ankles. The general nutrition appears good, although there seems to

have been recent loss of weight, evidenced by the hollow appearance of the cheeks and some wrinkling of the skin of the face; this is in contrast to the general obesity of the body.

Burns: The skin of the torso shows a burned area which covers most of the anterior surface of the body. The extent of the burn can be seen from the picture taken on the day before death (Plate XVIII). The burned areas are brilliant red where they are not obscured by islands of yellow-gray, greasy sloughing sheets of debris. The surface of the major portion of the burned area is moist and greasy (ointment) and appears granular on close inspection. The denudation is most severe in the right groin. Occasionally the transition from normal to burned skin is gradual and almost imperceptible to the naked eye, but in most places there is an abrupt change in color as well as in gross appearance of the skin. The edges of the burn show scaling of the dry and wrinkled skin. There is almost no hair on the burned area of the abdomen and only a very scant amount anteriorly on the thighs; the remaining body hair can be pulled out with ease. The skin of the scrotum is moist. There are edema and discrete areas of slight superficial ulceration, especially on the right side and in the anterior middle fold of the scrotum; there is practically no hair on the scrotum. The skin of the penis is intact anteriorly, whereas it is moist and superficially denuded in small spots posteriorly.

The gross appearance of the thoracic burn is similar to that of the abdomen. However, it appears that the burn here is not so severe and the ulceration not so deep as that on the lower abdomen. The severity gradually diminishes as it approaches the left breast. The major portion of the skin of the right chest wall is grossly intact. There are a few dry superficial excoriations around the right mammilla. These are covered with dry, crusty, scaly debris. Several similar dry desquamated yellow-green spots are found on the skin of the right anterior axillary fold, measuring 2 to 3 cm. in diameter. Hair growth on the chest is rather abundant except in the burned areas.

The skin adjacent to the burn shows a very intense, deep brown, punctate pigmentation, often conspicuously located around hair follicles. The individual pigment spots vary in size from a fraction of a millimeter to about 1 mm. in diameter. The degree of this pigmentation decreases with increasing distance from the burn. There is little pigmentation of the skin of the back except for scattered moles. There is extensive hair growth over the sacrum and both buttocks.

The skin of the anterior aspect of the neck from the level of the larynx down to about 1 cm. above the head of the sternum and to the clavicles on either side shows a uniform pale gray and faintly blue-brown color in a somewhat collar-like fashion. The skin here is dry and shows no gross lesions. However, hair is scant in this region.

Both hands are swollen and the skin of both shows very extensive lesions. There is far advanced dry gangrene of all fingers of the right hand, involving the two distal phalanges of each finger. The gangrenous portions are fairly sharply demarcated from the rest of the fingers. The thumb shows less extensive lesions than the second to fifth fingers. The surface of the gangrenous portion is black, dry and leathery, with many cracks and wrinkles, whereas the remainder of the burned area is opaque, whitish-gray and often yellow-green, and somewhat reminiscent of parchment paper. A few black-brown patches are noted here and there in the nongangrenous parts of the hand, particularly on the adductor side of the right thumb. The tip of the first finger of the left hand shows a small area of dry gangrene.

The burn involves the palmar and dorsal portions of both hands to about the middle of the wrist; in each case it is more severe on the volar surface than on the dorsal. The nails of all fingers of the left hand are grossly intact.

On the flexor side of each forearm the burn extends almost to the cubital fossa. The gross appearance of this lesion is quite different from that of the hands. It seems to be of a more recent date, resembling the burn of the abdomen. The surface is moist and granular and varies in color from pink to brilliant red. The desquamation of the skin appears quite deep near the wrist and seems more superficial toward the cubital fossa. The demarcation line is fairly sharp and the adjacent, apparently healthy skin shows a prominent diffuse and punctate brownish pigmentation. The marginal portions of the burn near the cubital region show desquamation and peeling of the skin, which is covered by dry scaly debris. Underneath this peeling skin there is red and edematous tissue.

Skin: The intact skin of the rest of the body is pale, with a slight but definite yellow tinge. The skin of the face is intact. It, too, is pale and slightly yellow. There is practically no growth of hair on either cheek, on the upper lip or on the anterior portion of the chin. There are a few short hairs under the chin and laterally under both mandibles. There is an edematous dark brown mole on the right cheek, measuring 6 mm. in diameter and 3 mm. in height. There is considerable hair loss over both temporal and parietal bones, as well as over the frontal portions of the scalp. The remainder of the scalp shows an abundant thick growth of dark, fairly short and curly hair.

Face: Both eyes show round and moderately dilated, equal pupils. The irides are brown. There is moderate loss of hair of both eyebrows and the remaining hair can be pulled out easily. The nose is not remarkable. The mucous membranes of the mouth are very pale, and there are several superficial, desquamative and ulcerative lesions covered with green-yellow exudate on the left and right sides of the buccal cavity. A lesion on the right side measures approximately 2.5 by 3.0 cm., while a lesion on the left side is more superficial and smaller. The teeth are in fairly good condition and repair. There are several fillings, primarily in the molar teeth. The mucosa of the tongue is pale and covered with a gray coating; the surface of the tongue is slightly furrowed, particularly at the base, and the papillae are prominent.

Thoracic Cavity

Both pleural cavities contain a small amount of clear yellow fluid. The parietal and visceral pleural surfaces are glistening and smooth on both sides. There are some apical adhesions on the right side and a few scattered adhesions posteriorly and at the base of the left lung.

The pericardial cavity is opened with some difficulty. There are a few cubic centimeters of a cloudy serofibrinous exudate in the little space that is left between the visceral and the parietal pericardium, for the pericardial cavity is largely occluded by a shaggy-fibrinous exudate. The exudate can be peeled off from some portions of the pericardial surfaces, revealing a shiny surface underneath.

Abdominal Cavity

The subcutaneous fat tissue is very conspicuous, measuring up to 4 cm. in thickness. There is a small amount of clear amber fluid in the abdominal cavity. The large intestine is distended with gas. The omentum covers the small intestine, the serosa of which shows blood-distended arborizing vessels in localized regions measuring up to 12 cm. in length. There are five such areas in the ileum. The color of the rest of the intestinal tract is a pale red-gray. The parietal and the visceral surfaces of the peritoneum, including those of the mesentery, are smooth and shiny and show no hemorrhages. The arrangement of the abdominal organs is not unusual. The spleen is soft and enlarged and the liver extends three fingerbreadths below the right costal margin. The diaphragm is at the level of the fifth rib on the right side and of the fifth interspace on the left.

Neck Organs

Only some of the neck organs have been obtained for examination. The lower part of the trachea and the bifurcation show no gross lesions. The lumen contains a small amount of frothy material and the mucosa is very pale. The lymph nodes at the bifurcation of the trachea are pigmented. They are normal in size, and are moist on sectioning. A small part of the thyroid shows colloid-containing parenchyma. The mucosa of the esophagus is intact and extremely pale.

Thoracic Organs

The mediastinal lymph nodes are of medium size and show spotted black pigmentation. They are rather dry on sectioning. The thymus is embedded in abundant mediastinal fat tissue, and no thymic parenchyma is grossly recognized on sectioning.

Heart: The heart is large, weighing 510 gm. The fibrinous exudate described earlier covers most of the surface of the heart. Occasionally there are shiny and glistening portions which are free of exudate, particularly over the right ventricle. The exudate is especially thick and abundant over the left ventricle, where it is accompanied by many hemorrhages, both punctate and confluent in character. Similar exudate, with and without hemorrhage, is found around the large blood vessels as they enter and leave the heart. The coronary vessels show no gross abnormalities. There are no thrombi in the pulmonary artery, which is opened in situ. However, after removing the heart from the pericardium, a round, rather firm, gray-yellow, thrombus-like mass measuring 1.5 cm. in diameter is found free in the pericardial cavity. Its origin is obscure.

The endocardium is smooth and delicate throughout both chambers. There is striking thickening of the endocardium over the interventricular septum. This is most conspicuous just below the aortic cusps and it diminishes toward the apex. The anterior portion of the free leaflet of the mitral valve is delicate and transparent, but there is some slight thickening of the posterior leaflet. The chordae tendineae are slender, thin and delicate. There are no gross lesions in the endocardium of the left auricle or of the auricular appendage, and no thrombi are seen.

The endocardial thickening of the interventricular septum, described in the foregoing paragraph, extends up to and involves the base and commissures of the aortic cusps. The free margins of the cusps are thin and delicate. There are a few small yellow plaques in the intima of the aorta at the entrance of the sinus of Valsalva and surrounding the mouth of the right coronary artery but not encroaching upon it. The endocardium of the right ventricle and auricle and the intima of the pulmonary artery are smooth, delicate and thin. The right ventricle and auricle are somewhat dilated. There are no thrombi in the right side of the heart. The ventricles and auricles contain clotted deep red blood which consists almost exclusively of cruor-type clot.

There is considerable thickening of the myocardium of both ventricles and also, to some extent, of the auricles. It is most conspicuous in the left ventricle. There is no grossly visible scarring.

Measurements

Tricuspid valve	12.0 cm.
Pulmonary artery	6.5 cm.
Mitral valve	9.5 cm.
Aortic valve	5.8 cm.

Thickness of myocardium

Left ventricle	1.8–2.0 cm.
Right ventricle	0.6–0.8 cm.

Aorta: The intima of the aorta is smooth and glistening. There are minute, slightly raised yellow plaques along the intercostal arteries. All vessels leaving the aorta are normal. The intima of the inferior vena cava and of the portal vein likewise shows no gross abnormalities.

Lungs: The lungs are very much alike in gross appearance. There are the aforementioned adhesions. The pleura of each lung is smooth and glistening. There are no subpleural hemorrhages. On sectioning, a fair amount of dark red fluid exudes from the lower lobes and from some portions of the upper lobes. The anterior parts of all lobes are air containing. The cut surfaces of the lower lobes are dark red with a slightly bluish tinge, while the remaining lung tissue is rather uniformly red-gray. Underneath the pleura of the right upper lobe in its midportion there is a small calcified and partially chalky nodule measuring 0.5 cm. in diameter. There is a partially calcified lymph node at the hilus. There is no evidence of consolidation. The bronchial and hilar lymph nodes contain anthracotic pigment and are not remarkable. The pulmonary blood vessels are intact. The mucosa of the bronchi is smooth and delicate.

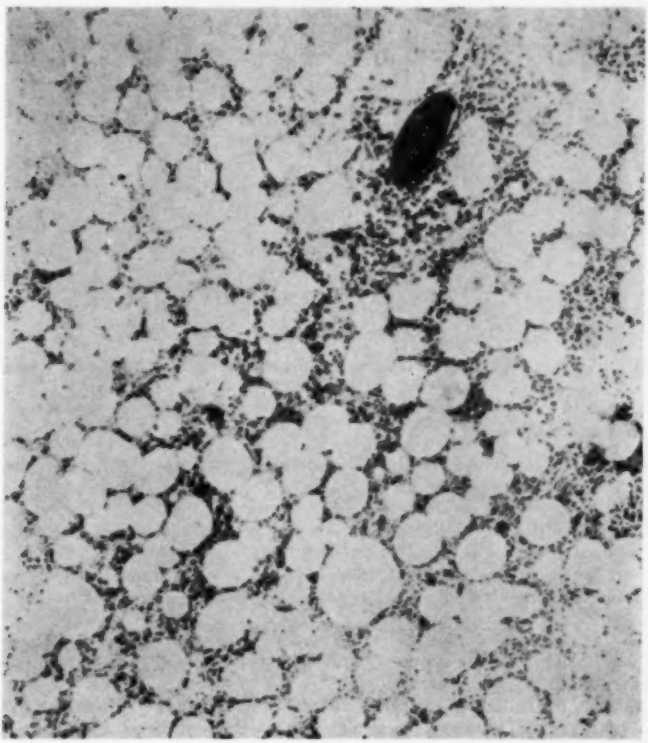

FIG. 20. Vertebral bone marrow showing hypocellularity and dilated capillaries.

FIG. 21. Vertebral bone marrow showing the maximum degree of cellularity seen in any of the sections.

Abdominal Organs

Liver: The capsule of the liver is smooth and glistening. There are two thickened scarred areas, measuring 2.5 by 3.4 and 4.0 cm., on the surface of the right lobe. The liver is large and of soft consistency; it weighs 1,860 gm. On sectioning, no gross abnormalities are noted, except for the general softness of the parenchyma. The color of the liver is deep brown with a tinge of dark red. The lobulation is indistinct but the periportal areas are clearly visible. The intrahepatic bile ducts are patent and contain liquid bile, and the branches of the hepatic blood vessels show no gross lesions.

The gall-bladder is distended with dark green viscous bile which mixes readily with water. The mucosa is smooth and velvety and the extrahepatic bile ducts are patent.

Spleen: The spleen is enlarged and soft, weighing 233 gm. and measuring 12.5 by 3.0 by 2.5 cm. The capsule is smooth and slightly wrinkled. On sectioning, Malpighian bodies are hardly visible. The red pulp is very soft and much of it can be scraped off with the edge of a knife. The trabeculae are not prominent.

Stomach: The mucosa of the stomach is prominently folded and pale gray-red. There is a moderate amount of mucus closely adherent to parts of the mucosa. There are no hemorrhages or ulcers.

Intestines: The small intestine contains bile-stained semiliquid material. The mucosa of the duodenum and the jejunum is intact and shows no hemorrhages or ulcers. The duodenum contains some bile-stained fluid. The Peyer's patches are very small. The aforementioned dilated blood vessels in portions of the ileum are clearly seen in the opened gut. There are no hemorrhages here. The mucosa everywhere is delicate and smooth. In the transverse colon, there is a roughened, ulcerated area covered with exudate and some blood. This ulcer measures 3.0 by 4.5 cm. and

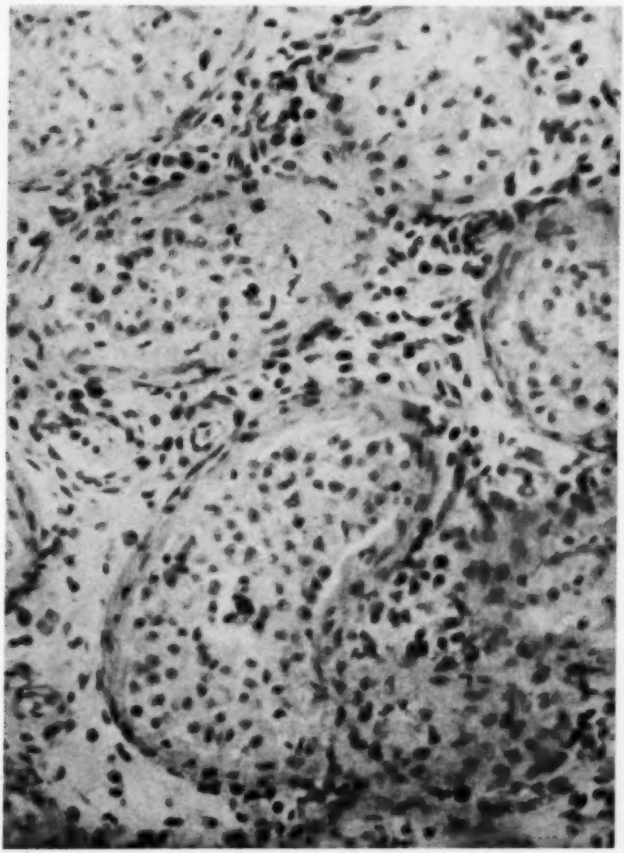

FIG. 22. Testicular tissue, the tubules of which are lined with Sertoli cells. A few necrotic lining cells are seen in the lumen of one tubule. The thickening and hyalinization of the basement membranes are conspicuous.

has irregular edges. The rest of the mucosa of the colon as well as that of the rectum is smooth.

Mesentery: The mesenteric lymph nodes are rather inconspicuous. They are deeply embedded in fat tissue and are small and gray-pink.

Pancreas: The pancreas is embedded in fat tissue and shows no abnormalities. The pancreatic duct is patent.

Adrenals: The adrenals are alike in gross appearance. Both are embedded in fat tissue. The cortex is pale yellow and the medulla is brown-gray and soft. The softening of the medulla is more advanced in the left adrenal.

Genitourinary Tract: The left kidney weighs 148 gm. and the right kidney weighs 155 gm. The measurements for each are 14.0 by 7.5 by 5.5 cm. The capsule of the left kidney strips off easily, while that of the right kidney is slightly adherent in two places. Beneath the capsule of the right kidney are two well circumscribed,

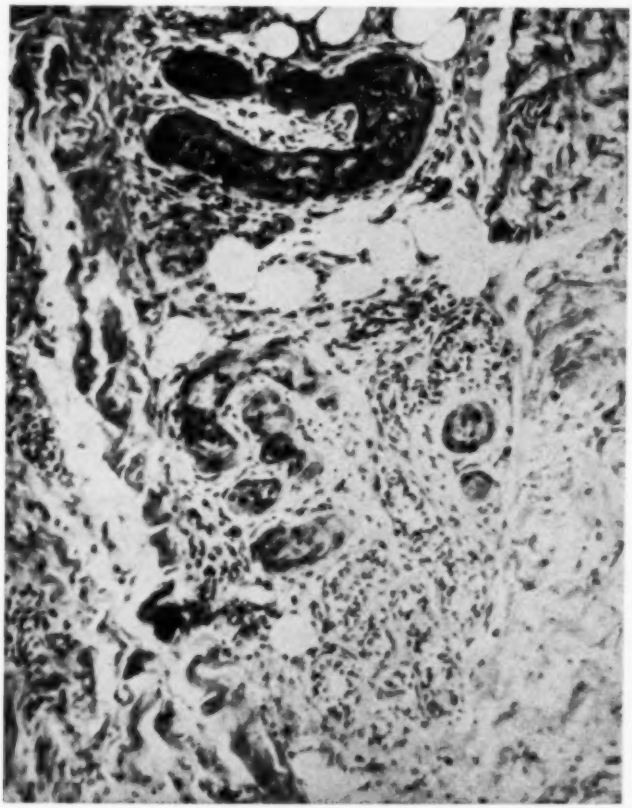

FIG. 23. Sweat gland of abdominal skin showing slight degree of dissociation of cells of secretory portion and advanced squamous metaplasia of duct epithelium.

FIG. 24. Dermal tissue of right hand showing disintegrating sweat gland and edema of the corium. Note thrombus in small blood vessel, the wall of which is necrotic.

somewhat elevated areas. These are yellow-gray, while the rest of the cortical tissue is dark red-gray. The blood vessels around the two yellow areas are injected. On sectioning, the two lesions are seen to extend into the parenchyma in a wedge-shaped fashion. The apices protrude into the medulla and are surrounded by a small zone of dilated blood vessels. The remaining parenchyma is intact. The cortices of both kidneys are dark red, while the medullae are pale gray with a tinge of red. The striations are not distinct in the cortex but the pyramids are well differentiated. In each case, the kidney pelvis is pale gray and the mucosa is intact. The ureters are patent and the linings smooth.

The bladder is contracted and contains about 20 c.c. of cloudy yellow-brown urine. The mucosa is wrinkled and pale and is not hemorrhagic. The ureteral openings are

patent. The wall is thickened and obviously contracted. The prostate is of normal size and shows no gross lesions. Both seminal vesicles contain viscous, mucoid gray-green material and are not grossly abnormal. The proximal portion of the urethra also shows no gross abnormalities. There are a few injected blood vessels in the otherwise pale, intact mucosa.

Testes: The testes are slightly smaller than normal. The parenchyma is pale brown. The epididymides and vasa deferentia show no gross abnormalities.

Blood-forming Tissues

The inguinal and axillary lymph nodes are swollen and very conspicuous. On sectioning, the cut surfaces appear pink-gray and moist, as do the retroperitoneal lymph nodes. The retroperitoneal fat tissue is abundant.

The bone marrow of the lower lumbar vertebrae is deep red and very soft. The marrow in the proximal portion of the diaphysis of the right femur is liquid and deep red. Only a small portion of the femoral bone marrow is examined.

The marrow of the crest of the right ilium immediately underneath the burned region of the overlying abdominal skin likewise is liquid and red.

Cranial Cavity

Not examined.

B. Gross Protocol and Selected Photomicrographs

Case 3

External Appearance

The body is that of a slender, athletically built, well developed young man whose age is given as 35 years. The body is in good nutritional state; it measures 168 cm. in length and the weight is estimated to be 65 to 70 kg.; it is still warm with the exception of both hands and about one-third of the forearms, which had been placed in ice during life.

Rigor mortis is present in the neck and is especially pronounced in the muscles of the jaws. There is beginning rigor mortis in both knee joints but none in the rest of the body. There is no gross evidence of edema except in the scrotum.

Skin: The skin is intact and its color is uniformly dark yellow with a slight bronze-brown tinge, particularly noticeable in the face. (It is of interest that about an hour after this observation was made the yellow discoloration had faded considerably and had given place at the end of the examination, about three hours later, to an ashen-gray color with only a slight yellow tinge. This transition was noted only in the skin of the face, whereas the rest of the body still retained the appearance described earlier.)

Livor mortis involves large portions of the skin in the form of irregularly outlined, small and large areas of bluish-purple. The discoloration fades promptly on pressure and reappears quickly with the release of pressure. It is particularly extensive on the dorsal and lateral aspects of the neck on the left side and involves the entire left ear. It extends down the back and involves both buttocks and the dependent parts of the lower extremities, with the exception of those areas which are in contact with the table. Similar but smaller patches of livor mortis also are noted in certain nondependent parts of the body: on both shoulders, the anterior chest wall and, to a lesser extent, on the abdomen and on both thighs.

Hair: There is no evidence of hair loss. The hair of the head is short and black with a sprinkling of gray, especially on the temples. Examination of the skin on both cheeks, the chin and the upper lip reveals an apparently normal amount of hair in the form of very short whiskers. The hair of both eyebrows is normal in density

and brownish-black. Hair growth is scanty about both mammae and moderate in amount in both axillae. The distribution of the pubic hair is male in type, and strands of it can be pulled out of the skin with greater ease and in greater amounts than usual. There is a wartlike dry thickening of the skin about 2 cm. below and medial to the right acromion anteriorly, measuring 5 by 3 by 3 mm.

Head: The features are regular. Both eyes appear to be sunken into the orbits. The sclerae of both eyes are dry and show a faint but distinct yellow tinge. There are two hemorrhages in the sclera of the left eye measuring 4.0 by 4.0 mm., and one hemorrhagic area in the medial aspect of the sclera of the right eye measuring 6.0 by 4.0 mm. The irides are deep brown, and both pupils are regular and round but somewhat dilated. The external auditory canals and nostrils are normal. The mucosa of both lips and of the gums is dry, very pale and slightly wrinkled. There are a few vertical fissure-like grooves in the gums of the lower and upper jaws but no ulcers are seen. The mouth cannot be opened because of severe rigor mortis. The teeth that can be examined appear to be in good condition.

Body: The abdomen is somewhat distended. There are purple-red hemorrhages in the skin of the abdomen, especially on the right side. These measure from less than 1 mm. to 2 mm. in diameter and occur singly or in small groups. Similar hemorrhages are noted in the skin on the right side of the thorax. There is a large subcutaneous hematoma in the right cubital region measuring about 15 cm. in length and up to 8 cm. in width. The skin here is a mottled, deep purple-blue.

The scrotum is edematous and enlarged; however, the skin is still wrinkled. It is moist in some places but no ulcerations are seen. Both testes are in the scrotum; they appear soft.

The skin of both arms has the same general appearance as the rest of the body. The right hand is cold, swollen and edematous. The edema involves primarily the palm and, to a lesser extent, the dorsum. All fingers are swollen but the skin retains some wrinkles. The skin of the whole hand, including the fingers, is mottled pale blue-gray up to the middle of the wrist joint onto the forearm in a semi-elliptical fashion for about 6 cm.

The left hand is decidedly more swollen than the right, and many blisters are noted. One large blister occupies a considerable portion of the thenar eminence and the palm, and extends upwards and outwards to the dorsum of the hand between the index and middle fingers. It measures about 4.5 by 8.0 cm. in diameter. There are eight more blisters between the fingers, most of which are filled with a clear yellow fluid. These blisters measure from 5 mm. to 2.5 cm. The color and gross appearance of the skin are similar to those of the right hand. No ulcerations are seen. The discoloration likewise extends to about the middle of the wrist joint on the dorsum, whereas on the flexor aspect it involves the forearm halfway to the cubital fossa in a semi-elliptical manner. There is a grayish, pale blue scar on the left side of the forearm about 4 cm. above the wrist joint.

On making the typical Y-shaped incision of the skin, blood exudes freely from all cut surfaces. There is no evidence of clotting except where blood remains in contact with exposed tissues for long periods of time (30 to 45 minutes).

Thoracic Cavity

The cartilage of both first ribs is calcified. On opening the thorax, many small hemorrhages are seen in the mediastinal fat tissue and in the parietal pleura on either side. There is very little free fluid in either pleural cavity and there are no adhesions. The surfaces are glistening and moist. The surfaces of the pericardium are shiny; the cavity contains about 50 c.c. of clear yellow fluid. In the parietal pericardium there are hemorrhages measuring from 1 to 4 mm. These are either single or in groups, especially near the reflection of the pericardium. Blood pours from the pulmonary

artery on opening it in situ. The mediastinal lymph nodes are small and inconspicuous; most of them are gray-pink. No thymic parenchyma is seen on sectioning the precordial fat tissue.

Abdominal Cavity

On opening the abdomen, distended and gas-filled loops of small intestine protrude from the incision. There are approximately 400 c.c. of a yellow-brown, slightly turbid fluid in the peritoneal cavity. The peritoneal surfaces are smooth and glistening. There are numerous petechiae in the parietal and visceral peritoneum, in the omentum, mesentery and pelvic cavity. The liver extends about three fingerbreadths below the costal margin and more to the left than usual. The dome of the diaphragm is in the fifth interspace on the right side and in the sixth interspace on the left. The stomach is distended with gas and fluid, and there are small petechiae in the serosa, especially in the pyloric region. The spleen is enlarged and soft. The appendix is in a retrocecal position. The intestines are uniformly distended with gas; they are flabby and mottled gray-red. The omentum is folded up in the left upper quadrant. The subcutaneous fat of the abdominal wall measures up to 2 cm. in thickness. Bloody fluid exudes freely from all cut surfaces.

Neck Organs

The lower portion of the trachea contains frothy material; its mucosa is intact but covered by a thin film of mucus slightly tinged with blood. The cervical lymph nodes are pigmented and small.

The distal third of the esophagus shows brownish-gray, intact mucosa. There is a small grayish-white membrane 3 cm. above the cardia, measuring 3 mm. in diameter. The rest of the neck organs are not obtained for examination.

Thoracic Organs

Heart: The heart is normal in size, weighing 315 gm. The epicardium is glistening and smooth throughout. Underneath it there are numerous fresh hemorrhages varying in diameter from less than a millimeter to 1 cm. These are located primarily along the course of the circumflex branch of the left coronary artery and on the anterior surface of the left ventricle. They are also very conspicuous under the epicardium of both auricles and in the subepicardial fat tissue at the base of the heart around the trunks of the great arteries and veins. A few scattered punctate hemorrhages are noted over the right ventricle. Similar, although fewer, foci of extravasated blood are seen in the endocardium. These are about equal in number in both ventricular chambers. There are some in the right auricle and none in the left. The endocardium of both auricles and ventricles is smooth, thin and transparent. The heart valves are intact and competent. There is a peculiar gelatinous edema involving about 2 cm. of the length of the free margin of the posterior leaflet of the mitral valve. This valve contains a prominent raised yellowish atheromatous plaque on the aortic surface measuring 1 cm. in length and up to 3 mm. in width. The chordae tendineae are intact. A considerable number of small hemorrhages are noticed in the myocardium at the apex of the left ventricle; only a few are noted elsewhere in the myocardium. Similar lesions are seen in the subepicardial fat tissue and myocardium of the right auricle.

The intima of the left coronary artery shows numerous yellowish raised patches of atheromatous material. Some of them are calcified. These changes are especially striking at the bifurcation of the left coronary artery. The right coronary artery is embedded in abundant fat tissue and shows no evidence of arteriosclerosis. Discrete and small pale yellow patches are seen in the intima of the arch of the aorta and in the

sinuses of Valsalva. The mouths of the coronary arteries are open and not encroached upon by arteriosclerotic changes.

Measurements	
Tricuspid valve	11.0 cm.
Pulmonary valve	6.5 cm.
Mitral valve	8.0 cm.
Aortic valve	6.0 cm.
Thickness of myocardium	
Left ventricle	1.6 cm.
Right ventricle	0.4–0.6 cm.

Lungs: The lungs are alike in gross appearance. They are very heavy and the pleura of each is smooth and shiny. The bronchi contain blood-tinged mucus which adheres to the mucosa; the latter is smooth and intact and shows scattered small petechiae. The smaller branches of the bronchial tree of both lower lobes and the

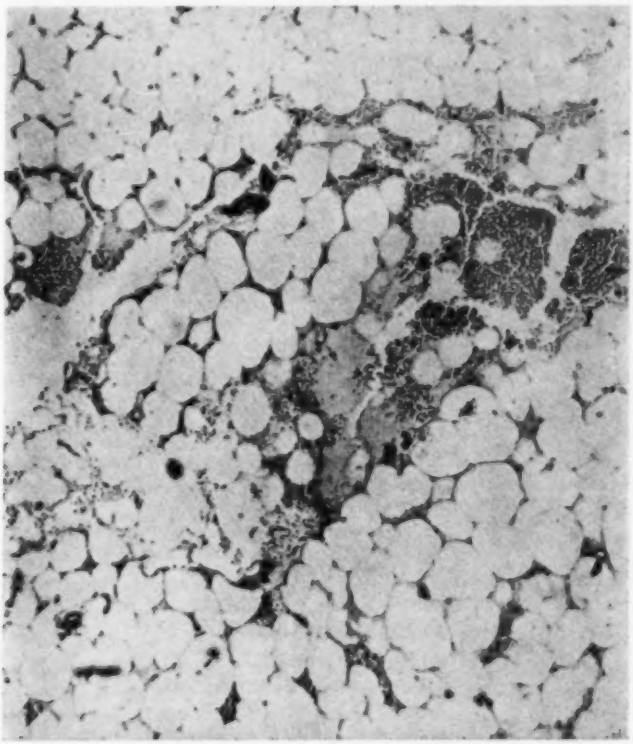

FIG. 25. Vertebral bone marrow illustrating practically complete aplasia with dilated sinuses, edema and hemorrhage. The islands of cells seen are extravasated red blood cells. No granulocytopoiesis is present.

posterior portions of both lungs contain acid-smelling brownish-gray fluid material similar in appearance to the stomach contents. The bronchial lymph nodes are deep blue-black and normal in size. The intima of the main branches of the pulmonary artery shows a few yellow patches measuring up to 3 mm. in diameter.

The major portion of the lung tissue of the right and left upper lobes is air-containing, and small patches of the anterior portions of the remaining parenchyma of both lungs likewise contain air. The remaining portions of the lungs are filled with fluid; much blood-stained liquid exudes from the cut surfaces. Many discrete foci of gray, granular consolidation are noted in both lower lobes. They measure up to 2 cm. in diameter and are quite prominent in the otherwise dark purple-blue lung tissue. The cut surfaces of both lower lobes have a striking sour odor.

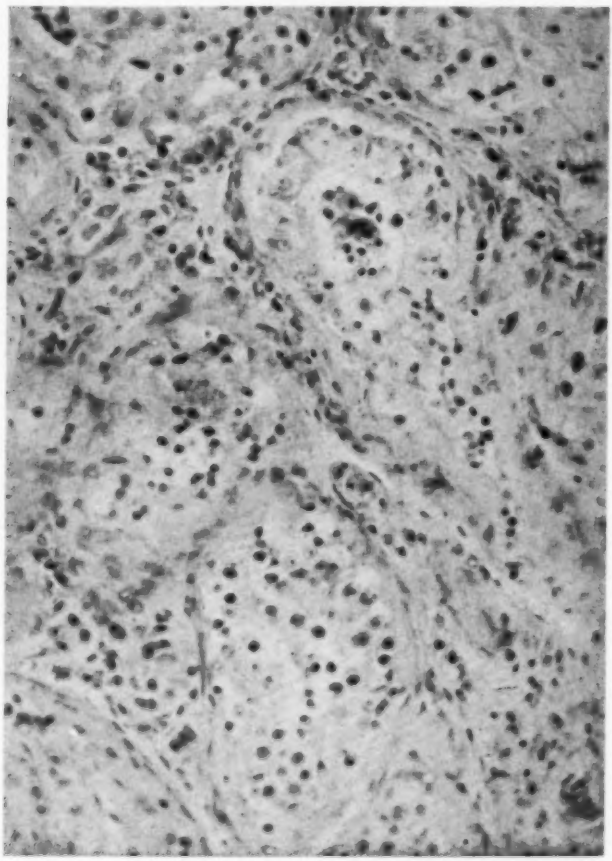

FIG. 26. Testicular tissue in which the germinal epithelium is markedly damaged. Necrotic spermatocytes and spermatozoa are seen in the lumina of the tubules. The absence of spermatozoa is striking.

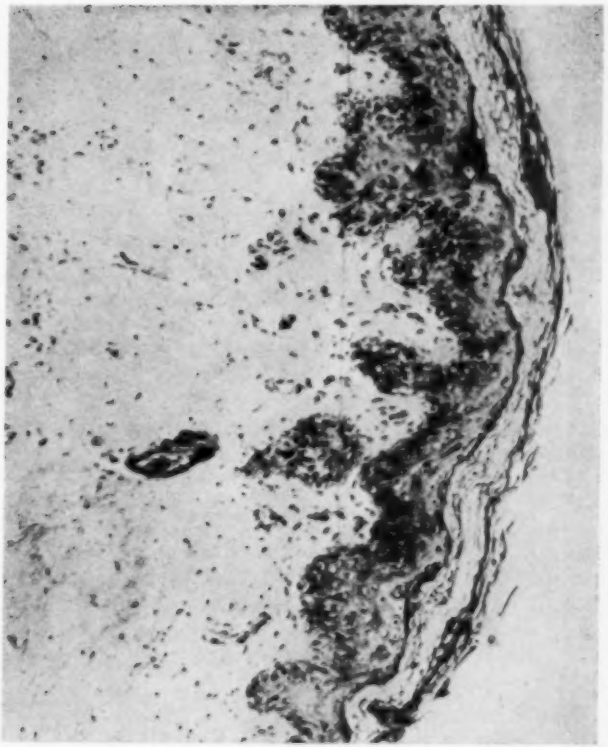

FIG. 27. Abdominal skin. Note the vacuolation of epidermal cells and the loss of normal stratification of cell layers. The dermal tissue is edematous.

The cut surfaces of both upper lobes are red-gray and most of the tissue here is air-containing.

Abdominal Organs

Gastrointestinal Tract: The stomach contains gas and a considerable amount of sour-smelling dark brownish fluid with amorphous granular material suspended in it. The mucosa is intact and is covered by a film of tenacious mucous material that is tinged with blood. Throughout the mucosa numerous dilated and blood filled small vessels are seen. These are especially striking in the fundus. There are scattered small petechiae. In the pyloric region more petechiae are seen and the mucosa is thrown into prominent folds.

There is a small amount of bile-stained fluid mixed with mucus in the duodenum and jejunum. The mucosa appears intact, and engorged blood vessels are again prominent. Of special interest are numerous discrete yellow and granular spots throughout the mucosa of the duodenum and the proximal portion of the jejunum; they measure from 1 to 3 mm. in diameter.

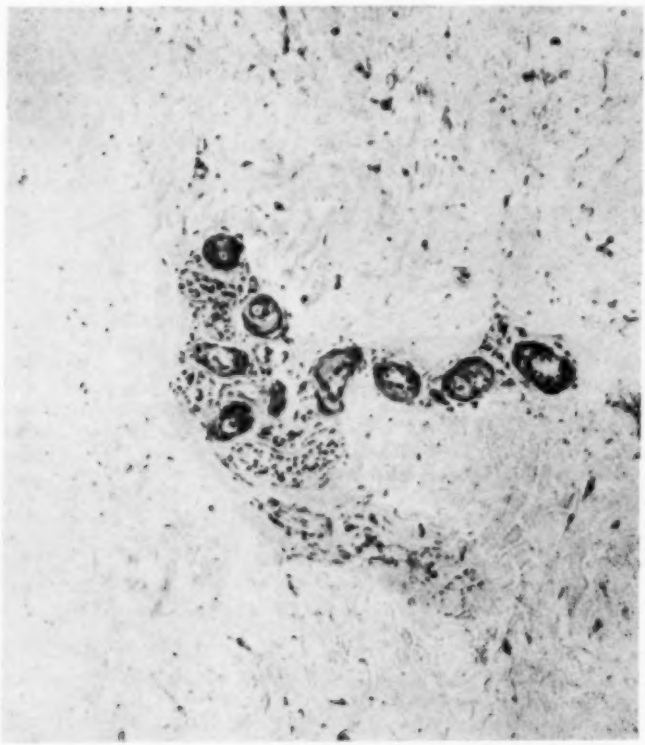

FIG. 28. Moderately advanced squamous metaplasia of duct epithelium of sweat gland in subcutaneous tissue.

The serosa of the whole intestinal tract is smooth and glistening. The intestine is filled with gas and sour-smelling semi-liquid material of dark brown color. There are scattered subserosal hemorrhages, especially in the ileum. The small intestine, as a whole, shows an extreme degree of congestion of blood vessels. The intensity of congestion varies from place to place. The distended blood-filled vessels are particularly striking in the duodenum, the jejunum and in the proximal part of the ileum.

The mucosa of the intestine is edematous in some places and intensely reddened. By far the major portion of this reddening is due to intravascular blood and relatively few hemorrhages are seen. However, some are observed in the jejunum which measure up to 1.5 cm. Scattered petechiae measuring 1 to 5 mm. are found in the ileum and in the colon. In the jejunum there are four isolated yellow-brown patches of soft, spongy consistency. These are 4 cm. or less in diameter. They are irregular in shape and outline, and measure up to 4 mm. in thickness. The remainder of the mucosa of the jejunum is either deep red or covered by irregular membranous patches of yellow-greenish exudate. This material covers large parts of the mucosa in continuous sheets in some regions, whereas in others, only the folds of the mucosa are

covered, and the intervening parts have an intense deep red color. Compared with the duodenum and jejunum, the ileum is moderately reddened and only few areas are covered with exudate. Hemorrhages not larger than 3 mm. are occasionally observed.

At the ileocecal junction the reddening is more intense and a few patches of greenish-gray exudate are seen. The mucosa of the cecum and of parts of the ascending colon is likewise reddened, due to intense engorgement of blood vessels of all sizes. The transverse colon is pale in comparison with other regions. A few discrete hemorrhages are seen in the colon, the largest being in the transverse colon and measuring 1.3 cm. in diameter. The mucosa of the sigmoid colon is again rather diffusely reddened and hemorrhages are more numerous. There are a few places where the mucosa is covered by greenish-gray exudate but no ulcers are seen.

The mucosa of the rectum is, in general, similar to that of the sigmoid colon, although the reddening is more intense and there is more exudate on the mucosa.

Mesentery: The peritoneal surfaces are smooth and glistening. The small blood vessels of the mesentery are prominently distended with blood, forming a striking arborizing pattern. Scattered about in the fat tissue are many purple-bluish lymph nodes, measuring from about 3 mm. to 1 cm. in diameter. On sectioning, most of them are pinkish-gray, but occasional lymph nodes show gross evidence of hemorrhage. No lesions are seen in the mesenteric arteries and veins.

Liver: The liver is enlarged, weighing 1,995 gm. and measuring 32 by 25 by 15.5 cm. The capsule is smooth and through it the mottled-brown color of the parenchyma

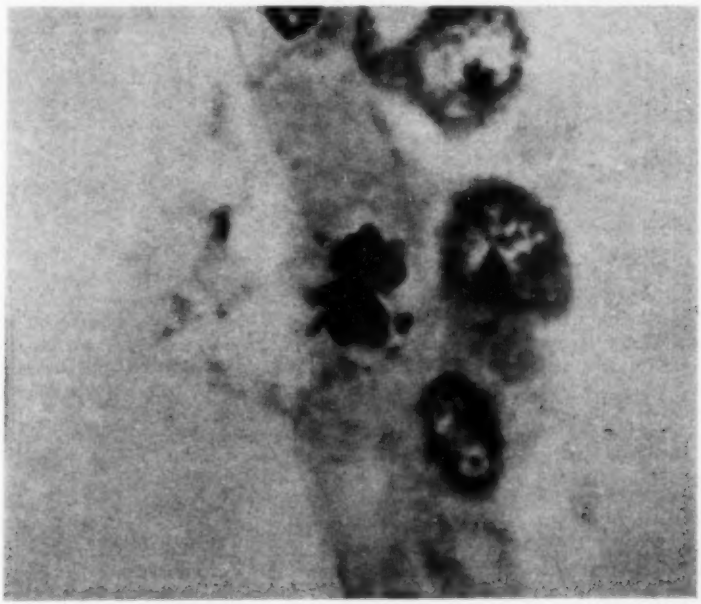

FIG. 29. Epithelial lining of crypt of small intestine showing a cell dying in mitosis. Note the free chromosome fragments in the cytoplasm. The other cell nuclei are swollen and show accentuation of chromatin material.

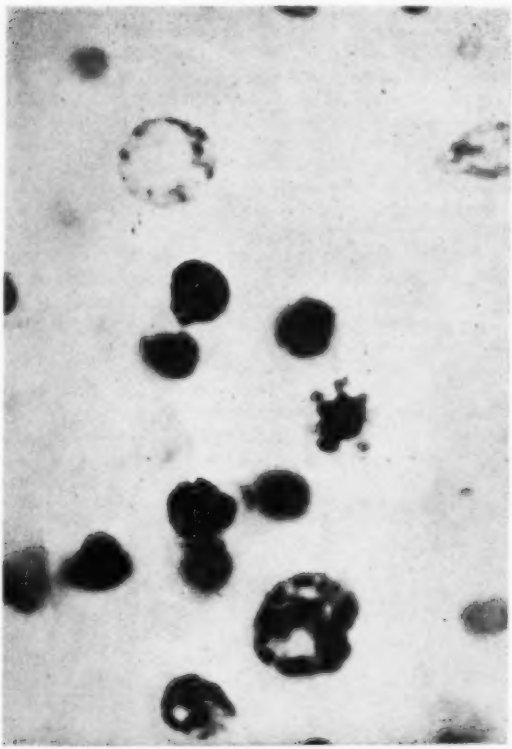

FIG. 30. Unidentified cell illustrating the "exploding" type of cell death referred to in the text.

can be seen. Much blood exudes from the cut surface. The parenchyma is soft and the lobulation distinct; the central veins stand out prominently, and the parenchyma around them is brownish-gray. The periportal areas are visible, and the bile ducts and blood vessels are patent.

The gall-bladder is distended and filled with dark-green viscous bile. The mucosa is smooth and velvety with streaks of white-gray. The extrahepatic bile ducts are patent and the mucosa is bile-stained.

Spleen: The spleen is enlarged and soft. It weighs 240 gm. and measures 14 by 9 by 3 cm. The capsule is slightly wrinkled and through it the deep purple-blue color of the parenchyma is seen. The cut surface shows a uniform deep red and reddish-blue color throughout. The trabeculae and blood vessels are clearly seen, but no Malpighian bodies can be distinguished. The splenic pulp is quite soft and the exuding fluid consists almost wholly of blood.

Pancreas: The pancreas is embedded in fat tissue. It shows no gross abnormalities. The pancreatic duct is patent and the lobulation well preserved.

Adrenals: Both adrenals are of normal size. The cortical zones show patchy yellow pigmentation, whereas the intermediate zones are light brown. The medulla is dark gray.

Genitourinary Tract: The left kidney weighs 190 gm. and measures 12.5 by 5.0 by 3.5 cm. The capsule strips with ease. There is an aberrant blood vessel entering the anterior surface. The surface shows numerous small depressed scars and faint remnants of fetal lobulation. There are a few bright yellow, circumscribed, nodular and slightly-raised areas measuring from 2 to 4 mm. in diameter. The remainder of the surface is deep red to reddish-gray, and the blood vessels are engorged.

On the cut surface the yellow nodular foci are seen to extend into the parenchyma of the cortex for distances of from 2 to 8 mm. The rest of the cortical tissue is intact. The pyramids are clearly seen and most of them show very distinct striations. However, some pyramids show compact and at times slightly streaked yellow areas at the apices. Some of these lesions measure up to 8 mm. in length and 4 mm. in width. The mucosa of the kidney pelvis is smooth. There are a few minute petechiae in the mucosa.

The right kidney weighs 155 gm. and measures 12.5 by 5.5 by 3.0 cm. The capsule strips less easily and is adherent in a few places. The gross appearance of this kidney is essentially the same as that of the left.

The urinary bladder is contracted and contains no urine. The mucosa is thrown into prominent folds; it is pale pink-gray and shows a few recent hemorrhages in the region of the trigone. The ureteral openings are patent and the mucosa of each ureter is smooth and intact.

FIG. 31. Epithelial cell in a crypt of the small intestine. The nucleus is dividing in an abnormal manner. This leads to cell death during mitosis.

The prostate is normal in size. There is a considerable amount of black pigmentation on the cut surface and at least one calcified concretion is encountered. The seminal vesicles are filled with gelatinous, greenish-gray material.

Both testes are of soft consistency. Their cut surfaces show a light brown parenchyma. The left testis and epididymis weigh 21 gm. The right testis and epididymis weigh 23.5 gm.

Blood-Forming Tissues

The bone marrow of the ribs, the sternum and the vertebrae is deep red and quite soft. A small portion of marrow from the upper third of the shaft of the femur contains very soft and gelatinous fat, with islands of red throughout. The lymph nodes of both axillae are small and pinkish-gray. No lymph nodes can be located in either groin in spite of prolonged search.

Retroperitoneal Tissues

The aorta throughout its course shows many raised yellow intimal patches. These are more numerous in the arch and in the thoracic portion than elsewhere. The aorta is quite elastic. There is no evidence of arteriosclerosis in the larger branches, such as the renal and mesenteric arteries. No lesions are seen in the inferior vena cava or in the portal vein. The retroperitoneal lymph nodes are palpable and, on sectioning, are gray-pink.

Skeletal Tissues

Large portions of the rectus abdominis muscle show a distinct yellow-gray streaking, and some portions of the thoracic musculature show similar changes.

Cranial Cavity

Not examined.

APPENDIX II

A. Statistical Analysis of Leukocyte Counts

Case 2

Time After Exposure	Pre-Exposure	No. of Counts	Neutrophils			Lymphocytes			Monocytes			Eosinophils		
			Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean
1 to 3 days	—	4	6122	1107	738	3783	1272	848	761	252	168	277	170	113
3 to 5 days		3	4939	893	348	2331	61	53	1013	283	245	251	53	75
8 to 10 days		4	4698	486	324	3096	1081	721	631	166	111	224	94	81
13 to 20 days		4	4889	694	463	3654	234	156	695	222	148	398	139	93
1½ to 2 mos.		2	5908	727	1028	3093	719	1017	730	52	74	217	74	105
3 to 4 mos.		3	5880	1860	1611	4170	210	182	809	171	148	297	28	24
5 to 6 mos.		5	5304	1618	904	2856	569	318	813	450	252	198	96	54
7 to 10 mos.		4	7168	2057	1371	3412	1025	683	672	215	143	367	154	103

Case 4

Time After Exposure	Pre-Exposure	No. of Counts	Neutrophils			Lymphocytes			Monocytes			Eosinophils		
			Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean
	Period I	7	3539	284	125	1482	305	135	393	124	55	167	61	27
	Period II	9	5004	1170	439	1821	326	122	524	218	82	189	81	30
1 to 3 days		6	8330	3140	1538	838	284	139	508	177	87	140	60	29
3 to 5 days		4	7237	1271	847	278	120	80	273	121	81	113	43	61
6 to 10 days		4	3578	958	639	473	247	165	417	88	59	280	105	70
10 to 15 days		5	4175	981	548	830	250	140	887	257	144	157	23	13
16 to 20 days		5	3560	1643	918	960	226	126	619	332	186	73	36	20
20 to 25 days		5	2535	340	190	853	107	60	321	64	36	74	31	21
25 to 30 days		5	2473	170	95	882	170	95	293	75	42	97	81	45
30 to 40 days		10	2462	243	85	1118	138	48	323	108	38	100	45	17
40 to 50 days		9	3154	219	82	956	124	46	600	171	64	71	45	17
55 to 70 days		5	4659	687	384	1071	219	122	434	120	67	51	20	28
2½ to 3 mos.		6	5015	722	354	1007	316	155	474	259	127	157	104	51
4 to 6 mos.		6	4392	751	368	1275	249	122	366	99	44	170	34	19
7 to 9 mos.		5	5390	710	397	1045	255	143	566	170	95	188	94	63
11 to 19 mos.		7	4964	1329	586	1293	485	214	656	104	46	229	84	47
2 years		1	5183			1988			568			71		

Case 6

Time After Exposure	Pre-Exposure	No. of Counts	Neutrophils			Lymphocytes			Monocytes			Eosinophils		
			Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean
	Period I	5	4377	546	305	2184	264	148	348	63	55	269	80	45
1 to 3 days		6	9606	1593	780	1173	195	96	1092	288	141	452	194	95
3 to 5 days		4	8705	1529	1019	814	292	195	713	101	67	332.8	68	45
5 to 10 days		4	5838	651	434	735	189	126	888	173	115	394	64	43
10 to 15 days		5	6200	1115	623	787	102	57	958	128	72	309	170	95
15 to 20 days		5	6964	566	316	1145	177	99	993	275	154	315	89	50
20 to 25 days		5	6611	226	126	1108	51	29	987	265	148	426.8	121	68
25 to 30 days		5	7084	1288	720	1081	366	188	1084	123	69	320	75	42
30 to 40 days		6	7244	1434	708	1314	253	124	965	188	92	437.7	218	107
40 to 55 days		5	6988	1082	605	1346	129	72	945	403	225	379	106	59
60 to 70 days		3	6966	249	216	1347	248	215	996	182	158	528.7	125	108
2½ to 3 mos.		4	7706	1486	991	1332	525	350	751	363	242	739	245	163
3½ to 4 mos.		4	6005	453	302	1168	345	230	759	294	196	732	434	289
4½ to 5 mos.		3	6820	2144	1857	1492	113	98	877	274	237	604	358	310
6 to 8½ mos.		4	7415	2082	1388	1308	268	179	631	193	129	553.8	243	162
9 to 12½ mos.		4	5612	1720	1147	1323	349	233	619	210	140	565	361	241
14 to 19 mos.		5	6380	694	388	1536	270	151	899	484	271	633	305	170
21 to 29 mos.		8	6210	1210	489	1246	258	104	690	193	78	392	243	107
2½ to 3 yrs.		3	6037	779	675	1817	435	368	660	243	210	498.7	187	162

APPENDIX II

A. Statistical Analysis of Leukocyte Counts

Case 7

Time After Exposure	Pre-Exposure	No. of Counts	Neutrophils			Lymphocytes			Monocytes			Eosinophils		
			Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean
1 to 3 days	—	6	7724	629	308	1360	356	174	876	361	177	336.8	177	87
3 to 5 days		4	7579	363	314	1059	249	216	772	196	170	274	128	111
5 to 15 days		4	4128	1085	723	1225	434	289	812	147	98	309.7	119	103
20 to 27 days		4	3829	968	645	1064	319	213	832	240	160	173	84	56
29 to 36 days		4	3251	536	357	1000	148	99	690	107	71	146	97	65
50 to 70 days		4	4022	736	491	926	175	117	551	155	103	190	205	137
9 to 18½ mos.		3	3170	276	239	1447	311	269	600	293	195	160	8	11

Case 8

Time After Exposure	Pre-Exposure	No. of Counts	Neutrophils			Lymphocytes			Monocytes			Eosinophils		
			Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean
	Period I	9	3190	843	296	2767	641	225	558	253	89	223	30	11
1 to 3 days		6	5812	1878	920	2435	572	280	960	398	195	588	259	127
3 to 5 days		4	3685	800	573	1552	235	157	564	130	87	327	71	47
5 to 15 days		3	3492	119	103	1206	214	185	672	55	48	247	61	53
20 to 31 days		4	3512	867	578	1506	270	180	756	98	65	312	208	139
34 to 38 days		3	3450	37	32	1783	92	80	772	82	71	328	40	35
50 to 77 days		5	3429	252	141	1564	392	219	557	199	111	378	177	99

Case 9

Time After Exposure	Pre-Exposure	No. of Counts	Neutrophils			Lymphocytes			Monocytes			Eosinophils		
			Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean
	Period I	9	3900	752	282	1698	239	90	532	141	53	207	45	17
	Period II	7	4556	1390	613	2259	283	169	405	135	60	314	101	45
1 to 3 days		6	5920	1900	931	1307	539	264	681	257	126	191	94	46
3 to 5 days		4	5675	1688	2387	1352	389	550	698	148	209	381	31	44
7 to 12 days		3	4196	267	231	1407	609	527	611	337	292	282	53	75
20 to 40 days		4	4095	336	224	2020	230	153	372	207	138	174	43	29
2½ to 5 mos.		4	4022	741	494	1775	501	334	638	44	38	323	220	147
6½ to 10 mos.		4	3575	882	588	1608	563	375	335	165	110	414	306	204
11 to 21 mos.		5	3786	447	250	1506	276	154	554	132	74	356	177	118

Case 10

Time After Exposure	Pre-Exposure	No. of Counts	Neutrophils			Lymphocytes			Monocytes			Eosinophils		
			Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean	Mean	Std. Dev.	Std. Dev. of Mean
	Period I	4	5690	1370	913	1770	158	105	592	111	74	166	48	68
1 to 3 days		6	9015	2796	1369	2476	774	379	1113	378	185	214	83	46
3 to 5 days		4	5361	1355	1916	1884	304	430	766	280	396	209	88	124
5 to 10 days		3	5055	1137	985	1342	153	132	702	194	168	103	72	102
15 to 25 days		5	5116	562	314	1460	343	192	767	246	138	148	67	37
28 to 42 days		3	5473	1098	951	1894	56	48	486	184	159	148	45	39
2½ to 3 mos.		2	5918	274	387	1813	179	253	719	55	78	344	344?	486?

APPENDIX II

B. Statistical Analysis of Erythrocyte Count and Hemoglobin Level
Case 4

Time Interval	Erythrocyte Count				Hemoglobin	
	No. Counts	Average Count (millions)	Standard Deviation	Std. Dev. of Mean	No. Counts	Average Hb. (grams)
−35 to −33 months	3	4.58	0.51	0.29	0	
−33 to −29 months	4	5.25	0.43	0.22	2	17.6
−29 to 0 months	7	5.28	0.56	0.21	8	17.15
0 to +10 days	14	5.43	0.64	0.17	15	17.96
+10 to +20 days	9	5.51	0.46	0.15	10	17.29
+20 to +30 days	10	4.98	0.27	0.09	10	17.3
+30 to +40 days	10	5.11	0.33	0.10	10	17.08
+40 to +54 days	9	4.53	0.12	0.04	9	16.99
+54 to +70 days	5	4.62	0.31	0.14	5	16.84
3½ to 4½ months	6	4.75	0.43	0.18	6	16.33
4½ to 6 months	6	5.18	0.25	0.11	5	17.40
7 to 9 months	5	4.84	0.33	0.15	5	17.68
10 to 19 months	7	5.34	0.36	0.14	7	17.37

B. Statistical Analysis of Erythrocyte Count and Hemoglobin Level*
Case 6

Time Interval	Erythrocyte Count				Hemoglobin	
	No. Counts	Average Count (millions)	Standard Deviation	Std. Dev. of Mean	No. Counts	Average Hb. (grams)
0.6 to +10 days	14	5.88	0.56	0.15	14	18.49
+10 to 25 days	15	5.67	0.20	0.05	15	17.67
+25 to +40 days	11	5.32	0.39	0.12	11	17.42
+40 to +70 days	8	4.91	0.35	0.12	8	17.86
3¼ to 4¼ mos.	4	5.50	0.29	0.15	4	18.25
4¼ to 7 mos.	7	5.34	0.36	0.14	7	17.63
7 to 9 mos.	5	5.66	0.32	0.14	5	18.94
10 to 19 mos.	8	5.70	0.61	0.22	8	19.55
20 to 32 mos.	8	5.82	0.31	0.11	8	20.69

* Blood counts prior to accident had all been done at sea level and are not comparable to these studies at an elevation of 7300 ft.

Appendix II

B. Statistical Analysis of Erythrocyte Count and Hemoglobin Level

Case 7

Time Interval	Erythrocyte Count				Hemoglobin	
	No. Counts	Average Count (millions)	Standard Deviation	Std. Dev. of Mean	No. Counts	Average Hb. (grams)
0 to +10 days	11	5.26	0.48	0.14	12	17.79
+10 to 25 days	4	5.43	0.19	0.10	4	16.72
+25 to 40 days	5	5.51	0.32	0.14	5	18.10
40 to 70 days	4	5.38	0.31	0.16	4	18.48
8 to 18 mos.	2	5.56	0.20	0.14	3	18.69

Case 8

Time Interval	Erythrocyte Count				Hemoglobin	
	No. Counts	Average Count (millions)	Standard Deviation	Std. Dev. of Mean	No. Counts	Average Hb. (grams)
−12 to 0 months	10	5.05	0.43	0.14	10	15.59
0 to +10 days	11	4.94	0.44	0.13	11	17.21
+10 to +25 days	4	5.07	0.17	0.09	4	16.58
25 to 40 days	5	5.50	0.47	0.21	5	16.92
40 to 70 days	5	5.21	0.32	0.15	5	16.70

Appendix III

A. Neutrophil Response

Time After Exposure	Pre-Exposure Average	Case 1	Case 3	Case 4	Case 6
	Period I* Period II	4954 (10 counts)	6830 (18 counts) 6360 (5 counts)	4302 (15 counts) 5280 (1 count)	4377 (5 counts)
1 to 1½ hrs.		6710 (1 hr.)	11610 (1 hr.)	6435 (1 hr.)	1 0335 (1½ hrs.)
6 to 12 hrs.		14580 (12 hrs.)	15400 (6 hrs.)	13098 (6 hrs.)	1 0311 (6 hrs.)
1 day		14306 12742	10616 14014	6593 4850	7125 7703
2 days		15345 15215	15041 22246	6765 12236	1 0894 1 1270
3 days		15379	15065	6208	1 0920
4 days		15586 17596	12725	9719	8511
5 days		13391	1105	7353	6608
6 days		9447 8697	279	5667	8782
7 days		5619 5087	277	3528	6980

* See Hematology in Presentation of Cases for explanation of Periods.

APPENDIX III

A. Neutrophil Response—*Continued*

Time After Exposure	Pre-Exposure Average	Case 1	Case 3	Case 4	Case 6
	Period I* Period II	4954 (10 counts)	6830 (18 counts) 6360 (5 counts)	4302 (15 counts) 5280 (1 count)	4377 (5 counts)
8 days		3905 3754	261	2487	5534
9 days		4418 4585	195	3190	5540
10 days		4920 4181		5105	5380
11 days		3754 3935		3663	4751
12 days		3935 3392		2944	5635
13 days		3570		4290	6000
14 days		5159 5011		4067	8114

* See Hematology in Presentation of Cases for explanation of Periods.

Appendix III

A. Neutrophil Response

Time After Exposure	Pre-Exposure Average	Case 2	Case 7	Case 8	Case 9	Case 10
	Period I Period II			4630 (4 counts) 3193 (10 counts)	4187 (16 counts)	5029 (3 counts)
1 to 1½ hrs.		7689 (1½ hrs.)	8944 (1 hr.)	8395 (1½ hrs.)	4687 (1½ hrs.)	8775 (1½ hrs.)
6 to 12 hrs.		6097 (12 hrs.)	7893 (7 hrs.)	6581 (6½ hrs.)	8227 (6 hrs.)	8237 (6 hrs.)
1 day		4559	7482	3648	6083	5218
		6142	7141	6900	4884	14615
2 days			7053	3024	3203	8340
			7828	6322	8437	8905
3 days		6169	7400	4556	7363	6716
4 days		4075	8085	3992	—	—
5 days		—	—	2255	—	4006
6 days		4573	7252	3938	3987	—
7 days		—	—	—	—	4257
8 days		4235	2950	3622	3850	6663
9 days		5220	—	—	—	—
10 days		5146	5883	—	4238	4244
11 days		4192	—	—	—	—
13 days		—	—	3520	4500	—
14 days		5180	3645	—	—	5320

B. Lymphocyte Response

Time After Exposure	Pre-Exposure Average	Case 1	Case 3	Case 4	Case 6
	Period I Period II	2029 (10 counts)	2250 (18 counts) 2625 (5 counts)	1651 (15 counts) 1980 (1 count)	2183 (5 counts)
1 to 1½ hrs.		3410 (1 hr.)	1161 (1 hr.)	1403 (1 hr.)	1457 (1½ hrs.)
6 to 12 hrs.		1296 (12 hrs.)	613 (6 hrs.)	814 (6 hrs.)	1105 (6 hrs.)
1 day		1553	0	522	1235
		208	151	793	1170
2 days		165	315	897	809
		322	0	599	1260
3 days		598	0	349	1235
4 days		422	0	470	587
		599			
5 days		748	11	75	932
6 days		443	9	219	502
		1338			
7 days		362	9	228	638
		266			

APPENDIX III

B. Lymphocyte Response—*Continued*

Time After Exposure	Pre-Exposure Average	Case 1	Case 3	Case 4	Case 6
	Period I Period II	2029 (10 counts)	2250 (18 counts) 2625 (5 counts)	1651 (15 counts) 1980 (1 count)	2183 (5 counts)
8 days		632 429	8	243	564
9 days		256 622	57	613	684
10 days		308 508		808	1053
11 days		183 322		659	970
12 days		322 63		504	713
13 days		345		808	813
14 days		536 819		948	680

B. Lymphocyte Response

Time After Exposure	Pre-Exposure Average	Case 2	Case 7	Case 8	Case 9	Case 10
	Period I Period II			2558 (4 counts) 2721 (10 counts)	1943 (16 counts)	1815 (3 counts)
1 to 1½ hrs.		5617 (1½ hrs.)	728 (1 hr.)	2415 (1½ hrs.)	1188 (1½ hrs.)	1638 (1½ hrs.)
6 to 12 hrs.		2125 (12 hrs.)	1730 (7 hrs.)	2384 (6½ hrs.)	686 (6 hrs.)	3520 (6 hrs.)
1 day		4171	1333	1856	1268	1617
		3218	1544	2875	1850	2775
2 days			1112	1701	710	1980
			1716	3379	2138	3315
3 days		2338	1341	1620	1741	2189
4 days		2359	735	1327	—	—
5 days		—	—	1353	—	1578
6 days		2247	1102	1906	963	—
7 days		—	—	—	—	1127
8 days		4728	1888	998	663	1422
9 days		3330	—	—	—	—
10 days		2490	1312	—	1402	1476
11 days		1834	—	—	—	—
13 days		—	—	1500	2155	—
14 days		3607	965	—	—	1749

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AECU—Unclassified reports originating within the Atomic Energy Project.
MDDC—Declassified reports released by the Manhattan Engineer District or by the Atomic Energy Commission before March 1, 1948.
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Case 1 (Plates I–XVIII)

(Plates III, V, VIII, XI, XIV, and XVIII by permission of *Surgery, Gynecology and Obstetrics*)

PLATE I. Dorsal view of both hands 42 hours after exposure. The nail beds of the right hand were slightly cyanotic. Note the blister on fourth finger of the right hand. The left hand was moderately swollen.

PLATE II. Dorsal view of both hands three and one-half days after exposure. The blisters were tensely distended with fluid.

PLATE III. Another view of both hands three and one-half days after exposure. The extremely large bulla on the palm of the right hand can be seen in this view.

PLATE IV. Dorsal view of the right hand after débridement on the ninth day. The superficial layer of the dermis was dark red with small areas of hemorrhage. The skin of the back of the hand was pallid and mildly cyanotic. The pitting edema of the dorsum of the hand can be seen.

PLATE V. Palmar view of the right hand nine days after exposure. The epidermis has been cut away. There was no blanching of the dermis of the palm on pressure. The fingers felt quite cold to the touch. No radial pulsation could be felt.

PLATE VI. Dorsal view of the right hand 15 days after exposure. The fingers were dark red in color with patches of black, dry gangrene. The nails of the thumb and first finger had been removed. The edema of the back of the hand is still evident. The epidermis over the knuckles had been lost, exposing the dermis which was pink in color and warm to the touch.

PLATE VII. Palmar view of the right hand 15 days after exposure. The dermis of the palm was drier than before. It was light red in color with small areas of reddish black. The palm was still warm to the touch.

PLATE VIII. Dorsal view of the right hand 24 days after exposure. The dry gangrene of the fingers showed marked progression. The dorsum of the hand was covered by a thin layer of fibrin.

PLATE IX. Palmar view of the right hand 24 days after exposure. The contraction of the fingers is evident. The tissues of the palm and wrist were quite pale in color as a result of ischemia and necrosis.

PLATE X. Palmar view of the left hand nine days after exposure. The cyanotic area at the base of the thumb can be seen in this picture.

PLATE XI. View of the left hand 15 days after exposure showing the blister that involved the palm, thumb and forearm. The forearm is less swollen than before.

PLATE XII. Same view of the left hand after the removal of the epidermis 15 days after exposure. The dermis was light pink in color but showed no hemorrhagic areas.

PLATE XIII. Dorsal view of the left hand 24 days after exposure. The color of the dermis was still pink, with evidence of good circulation. The desquamation extended up to the wrist.

PLATE XIV. Palmar view of the left hand 24 days after exposure, showing the dark red, gangrenous color of the thumb. The nails were still in place.

PLATE XV. Torso and lower part of the face 12 days after exposure. This picture shows the stomatitis and abdominal distention. The white membrane on the edge of the tongue can be seen. The erythema of the trunk can be seen in this picture.

PLATE XVI. Close-up of the face 12 days after exposure. This picture gives a better view of the membrane on the tongue and of the cracking at the corners of the mouth. It also shows the pigmented naevus on the right cheek.

PLATE XVII. Right side of the head 20 days after exposure showing loss of beard and hair on the temple. The condition of the lips had improved. The naevus on the right cheek was slightly smaller than before.

PLATE XVIII. View of the abdomen 24 days after exposure showing complete loss of epidermis. The dermis was salmon-pink in color and was still covered by a small amount of fibrin. Note the decrease in amount of axillary hair. The loss of hair of the upper chest, although marked at this time, does not show up well in this picture.

Case 3 (Plates XIX–XXIV)

PLATE XIX. Dorsal view of the left hand three days after exposure. The blisters between the fingers are well visualized. The skin of the dorsum showed a patchy type of cyanosis as a result of the refrigeration of this extremity.

PLATE XX. Palmar view of the left hand three days after exposure, showing blisters on the palm and thumb. The skin of the hand was quite cyanotic with signs of early gangrene on the tip of the thumb.

PLATE XXI. Dorsal view of the left hand nine days after exposure. The swelling had decreased slightly. There had been little, if any, extension of the blisters.

PLATE XXII. Palmar view of the left hand nine days after exposure. The skin was pallid and very cyanotic. There had been some extension of the blister on the palm of the hand. The blister on the thumb had lost its fluid.

PLATE XXIII. Dorsal view of the right hand three days after exposure. The swelling had extended up the forearm. The skin of the fingers was moderately cyanotic.

PLATE XXIV. Dorsal view of the right hand nine days after exposure. The skin was intensely cyanotic. No blisters had been formed. There was a slight decrease in swelling.

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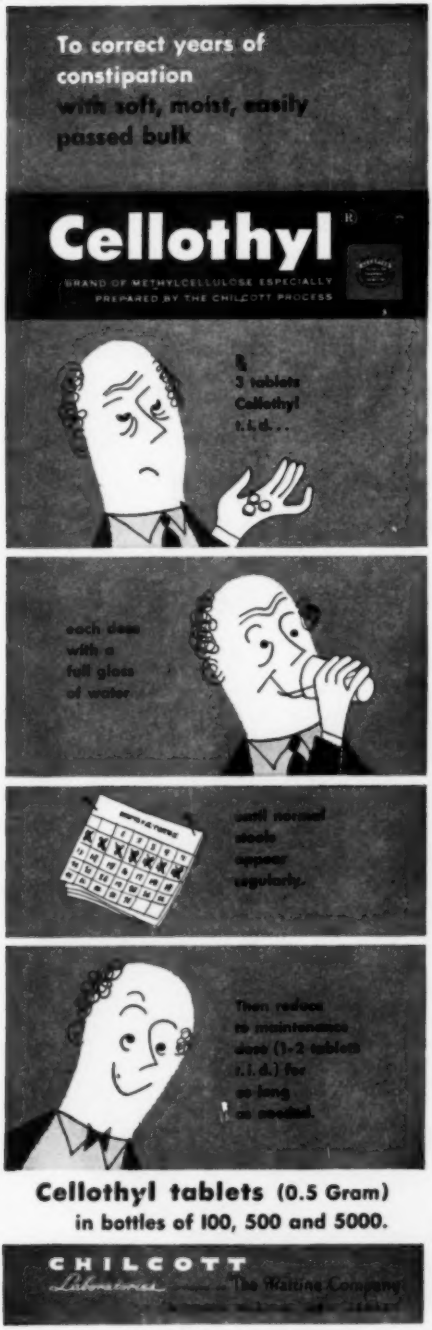
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1. Newey, J. A., and Goetzl, F. R.: Permanente Med. Bull. 7:67 (July) 1949.

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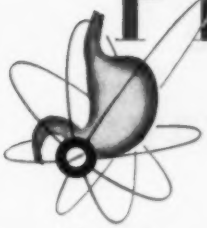

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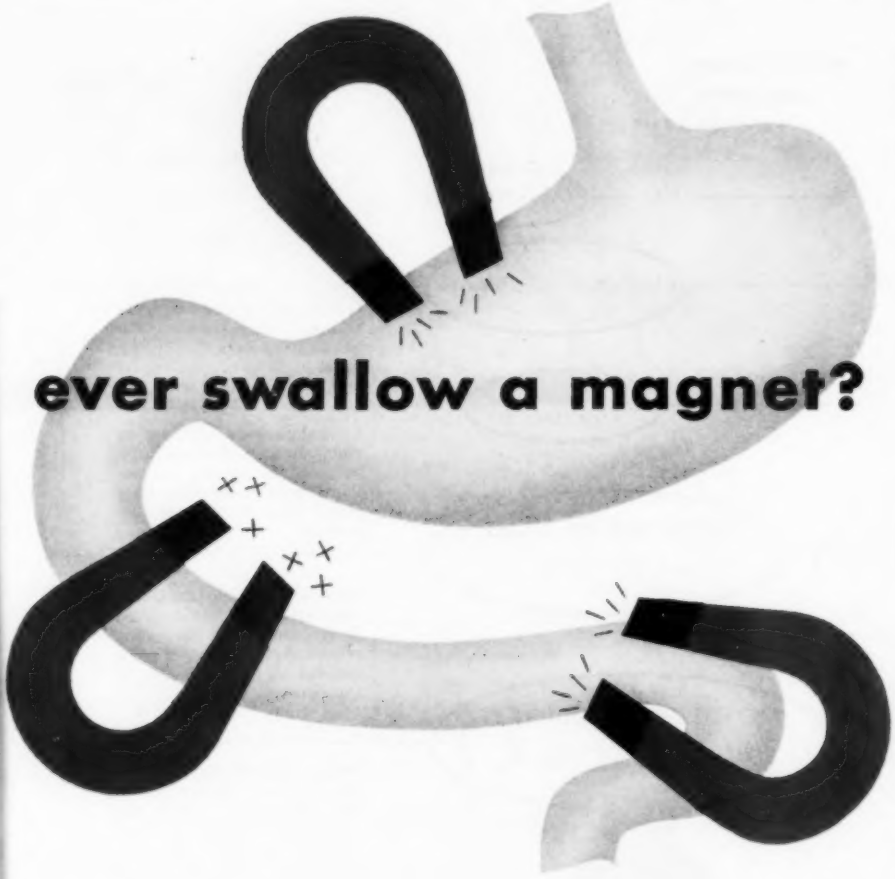

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NATRINIL – the CATION-exchange resin. For sodium withdrawal. Indicated in CONGESTIVE HEART FAILURE, EDEMATOUS STATES, HYPERTENSION.

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In peptic ulcer . . .

RESINAT "brings quick relief of ulcer pain and speeds the healing"[1] . . . without gastrointestinal side effects.[2]

How?

RESINAT is an anion-exchange resin and its molecules act much like magnets in the body. The action is this . . . in the stomach the resin molecule binds and withdraws the hydrochloric acid and pepsin.[3] These substances, bound to the resin, are carried into the small intestine where they are dropped off. The acid is promptly neutralized by intestinal alkalinity and pepsin is inactive.[4]

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(polyamine-methylene resin)

The Original Medical Application of Anion-Exchange Resins

does	**does not**
relieve pain quickly	**remove chlorides, phosphates**
normalize excess acidity	**minerals or vitamins**
inactivate pepsin	**alkalinize the system**
promote rapid healing	**cause constipation or diarrhea**

and is non-toxic

RESINAT is indicated in the treatment of peptic ulcer, and for the relief of hyperacidity, gastritis, heartburn, and certain forms of colitis.

Available: Tablets, 0.5 gram, bottles of 36, 100 and 1000.
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Powder in one gram individual packets, boxes of 50 and 100 packets.

Dosage and administration: In acute and chronic ulcer, one-half gram (1 tablet or 2 capsules) every two hours while awake. Much larger initial doses may be necessary to obtain relief.

1 Spears, M. M., and Pfeiffer, M. C. J.: Gastroenterology **8**:191 (Feb.) 1947.
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REFERENCES: 1. Day, T. J. et al.: Proc. Staff Meetings Mayo Clinic 21:497, 1946. 2. Hoagland, R. J.: Am. J. Med. Sci. 9:272, 1950. 3. Smith, R. T.: J. Lancet 70:192, 1950.

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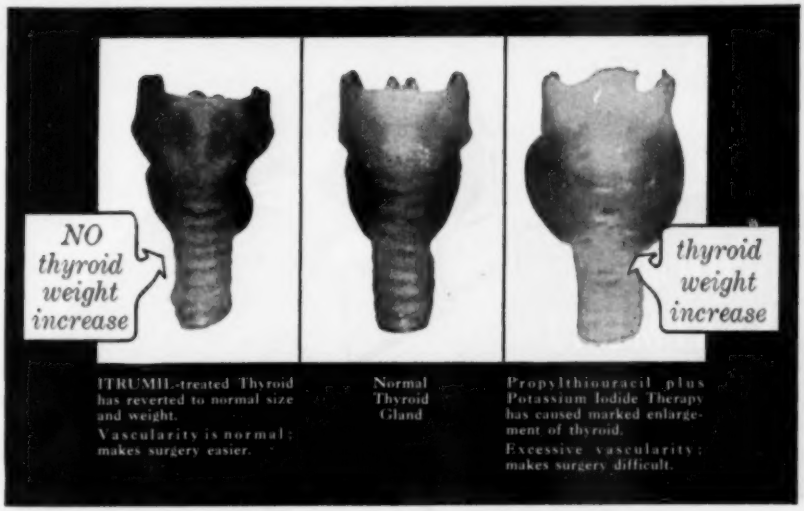
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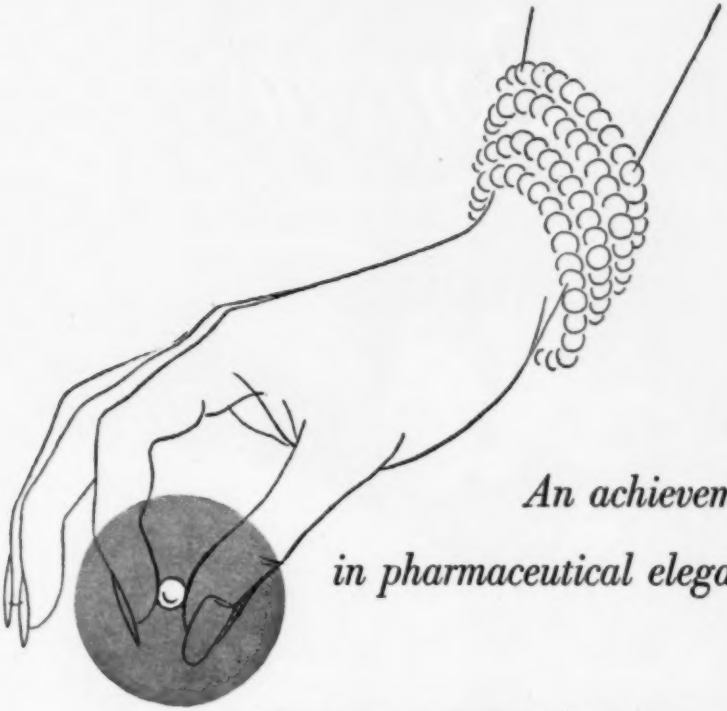

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NORCROSS, B. M., *N. Y. State J. Med.* **51**: 2356, Oct. 15, 1951.

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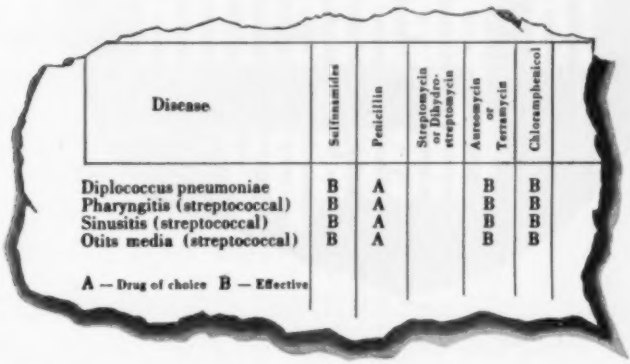

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*KEEFER, C.S., POSTGRAD. MED. 9 101, FEB. 1951

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1. Kadison, E. R.; Ishihara, S. J., and Waters, T.: A New Form of Penicillin with Anti-Allergic Properties, Am. Pract. & Digest Treat. 2:411 (May) 1951.
2. Longacre, A. B.: P-92 Penicillin; Report of a Very Low Reaction Rate in Therapy with a New Penicillin Salt, Antibiotics & Chemotherapy *1*:223 (July) 1951.

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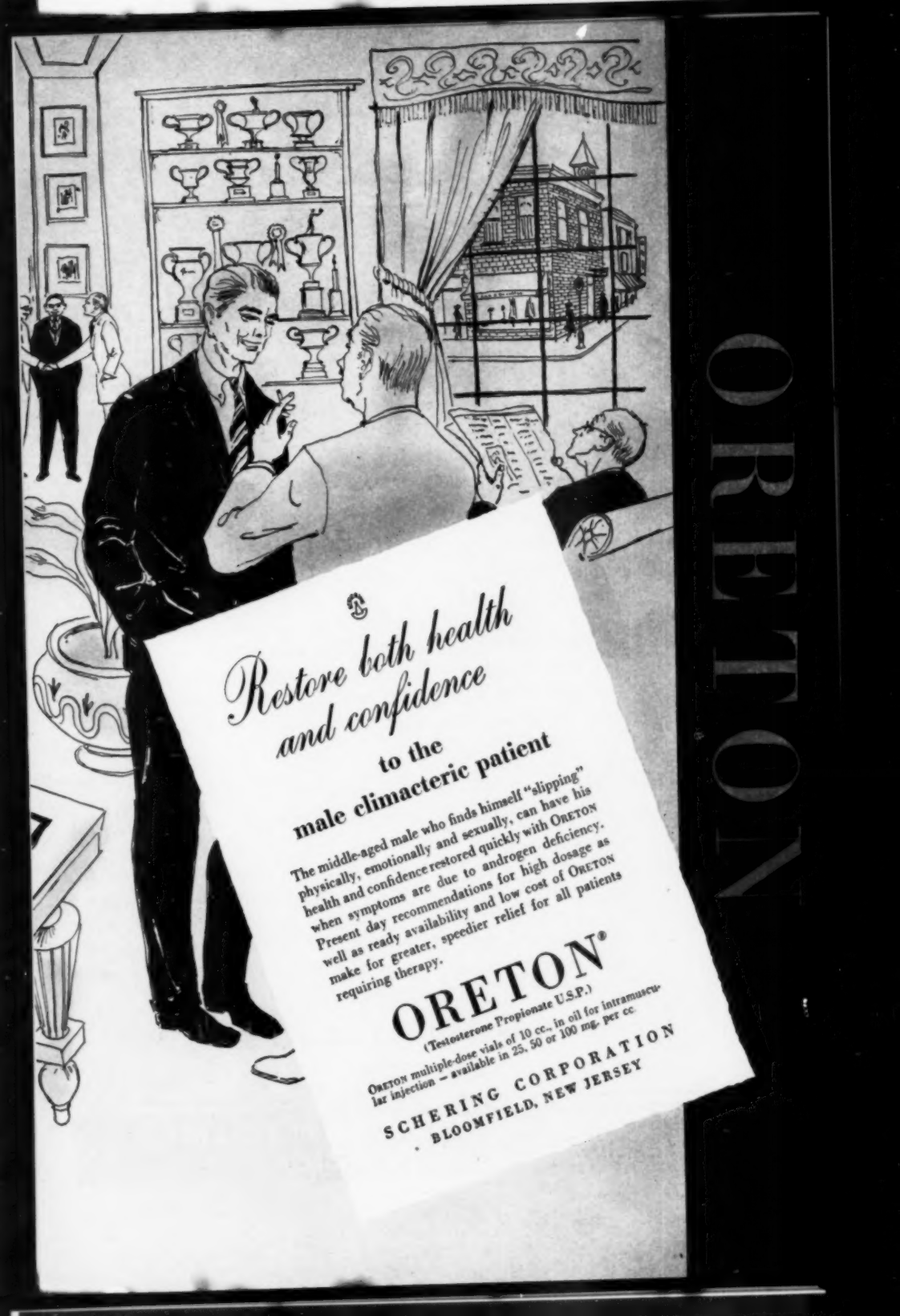
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REFERENCES:

Ray, H. M.: Am. J. Digest. Dis., 14:153, 1947.
Shapiro, S.: Ibid, 14:261, 1947.

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1. Best, C. H.; Lucas, C. C.; Patterson, J. M., and Ridout, J. H.: Lipotropic Properties of Inositol, Science *103*:12 (Jan. 4) 1946.

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4. Cogswell, R. C.; Schiff, L.; Safdi, S. A.; Richfield, D. F.; Kumpe, C. W., and Gall, E. A.: Needle Biopsy of the Liver, J.A.M.A. *140*:385 (May 28) 1949.

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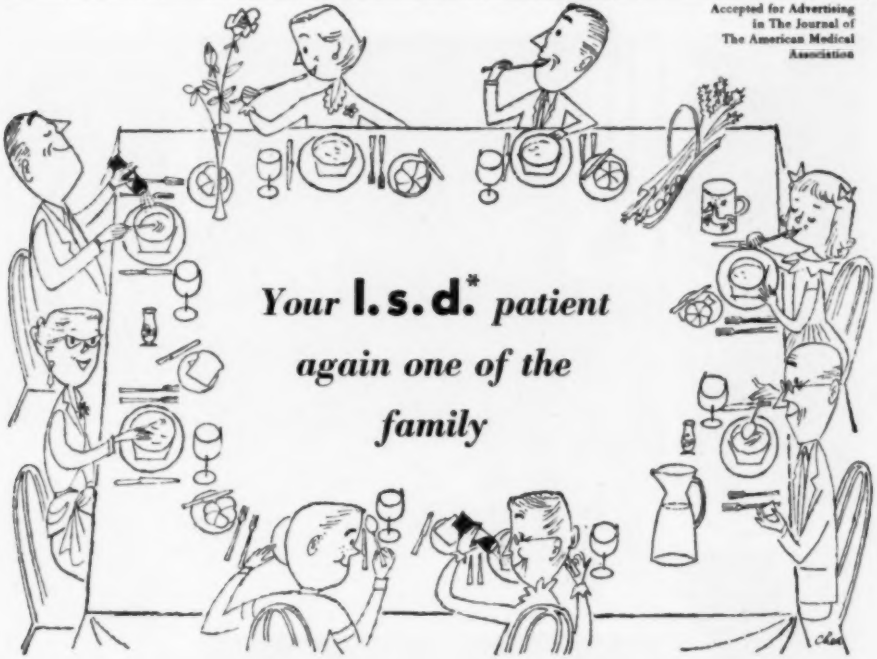

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1. Rimmerman, A.B., and Halpern, A.: A comparative study of sodium-free salt substitutes, Am. Pract. & Dig. Treatment 2:168 (February) 1951.
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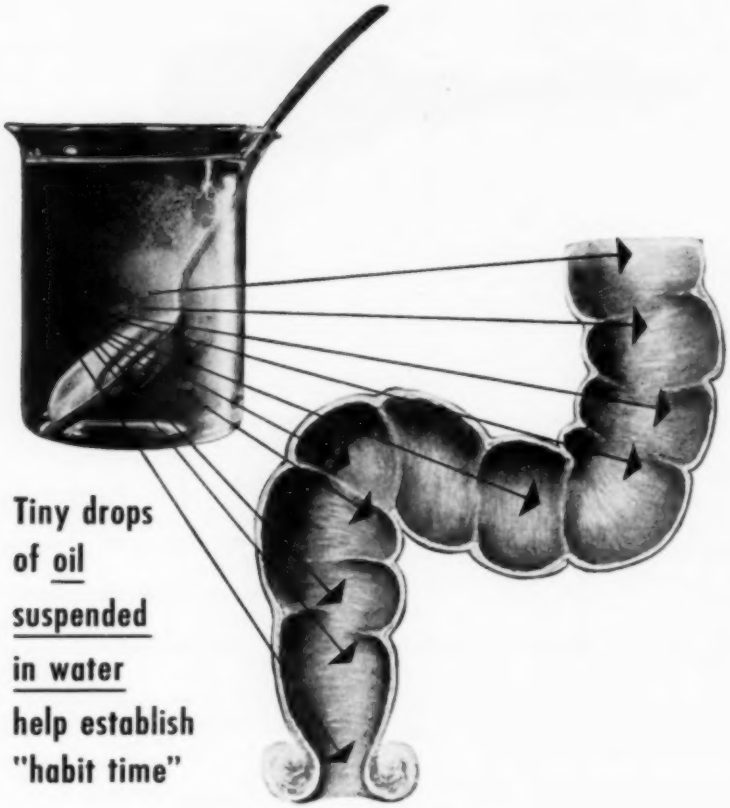

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1. Mann, G. V., and Stare, F. J.: Nutritional Needs in Illness and Disease, in Handbook of Nutrition, ed. 2, published for American Medical Association, Philadelphia, The Blakiston Company, 1951, chap. 17, p. 351.

2. Sherman, H. C.: The Nutritional Improvement of Life, New York, Columbia University Press, 1950.

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1. THIELE, G. H.: Southern Med. J. *35*:920 (Oct.) 1942.

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2. Wang, K.J. and Grossman, M.I. Am.J.Phys. 155:476,1948.
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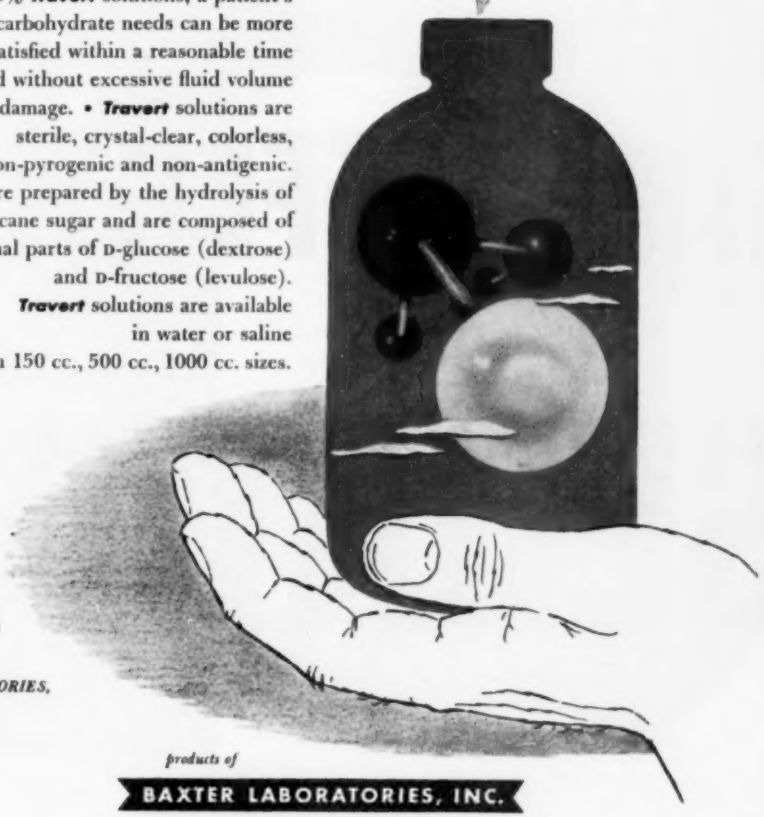

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ANNALS OF
INTERNAL MEDICINE

VOLUME 36 FEBRUARY, 1952 NUMBER 2, PART 2

ANIMAL DISEASES OF PUBLIC HEALTH SIGNIFICANCE *

By JAMES H. STEELE,† *Atlanta, Georgia*

THE relation of disease in animals and man has been recognized for thousands of years. The earliest observations were recorded by the Egyptian physicians who administered to the ills of animals as well as to those of man. They had three theories for disease—meteorologic, magic and gastroetiologic. The third theory is supported by observations that those who ate the flesh of sick animals became ill themselves. Later the Greek and Roman physicians described the transmission of disease from animals to man by contact, e.g., rabies, and the similarity of the lesions, e.g., anthrax. All of the early Mediterranean countries practiced meat inspection. The exchange of external parasites between man and animals was observed by the Arabic medical recorders.

During the Middle Ages disease was attributed to all kinds of agents. There were no attempts to control infection until after the Crusades, when quarantine was inaugurated which was directed toward animals, e.g., sheep pox, as well as man. In the fourteenth century meat inspection was established in Germany to control measly pork. Previously the French government had had meat inspection in the large cities. During the succeeding centuries there were many changes in meat inspection, and often it was discontinued because of wars, and various interpretations as to its value. On the other hand, there were reports without supporting evidence, that certain diseases of man were contracted from animals. Among these was syphilis. In the eighteenth century the lesions of bovine tuberculosis, especially those on the serous membranes which begin as reddish soft granulations and enlarge into nodules on the pleura, were thought to be a cause of syphilis.[1] Following the experiments of Graumann involving the transmission of syphilis, meat inspection was dropped in many parts of western

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 12, 1951.

† Veterinary Director, Communicable Disease Center, Public Health Service, Federal Security Agency, Atlanta, Georgia.

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Europe. It was not reëstablished until it was demonstrated by Kuchenmeister and Paget in the mid-nineteenth century that pork tapeworm and trichinosis were transmitted to man by contaminated pork products.

The evidence of the transmission of animal diseases by routes other than ingestion was presented by Jenner in the case of cowpox in 1796, and by Zinkle in 1804 when he demonstrated that the saliva of rabid dogs was infectious. Anthrax was shown by Pollender in 1849 to be an infectious disease of both man and animals, and this was later confirmed by Davaine. The relation of animal-borne diseases to human health was further supported by the brilliant investigations of the founders of bacteriology.[2, 3, 4]

Epidemiologic studies of tuberculosis of children revealed that the tuberculous cow and its contaminated milk were threats to human health. This problem more than any other emphasizes the interrelation of the health of man and animals. It has also shown what can be done to eradicate such diseases as bovine tuberculosis in man.

The present day problem of the relation of animal diseases to human health is much more complicated than previous investigations indicated. These diseases can be divided into three categories as to their effect upon man:

1. The animal diseases which are communicable to man. There are more than 80 in this group, as reported by the WHO Group on Zoönoses. They include viral, rickettsial, bacterial and parasitic diseases.

2. The diseases of animals which are not considered a direct threat to the health of man, such as rinderpest, swine cholera, contagious pleuropneumonia and bird malaria, but to jeopardize his economic welfare. These diseases affect the health of large populations by the loss of essential protein foods, such as milk, meat and eggs, and cause shortages of other animal products that affect the well being of man, including wool, hides and medical products. The increased price of these animal products from losses due to disease also has its effect.

3. The third category is made up of 1 and 2 and consists of diseases of lower vertebrates which may adapt themselves to man. The theory that the infectious diseases of the lower forms of life are struggling to adapt themselves to higher forms of life has been suggested by Burnet [5] and supported by Meyer.[6] If these diseases are attempting to adapt themselves to a wider and higher host range, we have a difficult road ahead. Man has been able to adapt a number of diseases to new hosts in the laboratory, but these have not always been adaptations to more highly developed mammals.

The animal diseases transmissible to man have certain characteristics common to the entire group. Some of these are: 1. Infection in man is usually limited to the diseased individual, and there is seldom person-to-person transmission. 2. The clinical and anatomic character of the disease in man is similar to that in animals, provided the portal of entry is the same. 3. The highest incidence occurs in individuals whose occupations bring them into close contact with animals or animal products.

Previous writers on this subject have divided the diseases found in animals that are transmissible to man into the following groups, according to the classification of the etiologic agents: (1) virus, (2) rickettsia, (3) bacteria, (4) fungus, (5) protozoa, (6) helminth, (7) arthropod and (8) toxin-produced diseases.[10, 11] In our discussions we will try to point out the characteristics of a prototype disease of each of the above groups.*

In this virus group, rabies is the most important disease as far as human health is concerned. Other viral diseases of animal origin, such as the arthropod-borne encephalitides, psittacosis and jungle yellow fever, are important to the health of certain countries and would be a serious threat to parts of the world where they do not exist. Japanese B encephalitis and Venezuelan equine encephalomyelitis could be disturbing problems in the United States, to both animal and human health. Rabies is worldwide except for Australia, certain Pacific and Atlantic islands, Great Britain and Scandinavia. It has been described for thousands of years and its transmission from animals to man recognized. The disease has been observed in North America since the eighteenth century, when it was described in dogs and foxes. The disease has been eradicated from certain areas, such as Great Britain, Scandinavia, Holland and Belgium, by animal control. The Pacific islands and Australia have never had the disease and have kept it out by strict quarantine.

In the United States it has been difficult to control rabies by animal control for many reasons, one of the more pertinent being that there is considerable sentiment for dogs, and popular opinion allows them the unfettered freedom of the streets or the countryside.[12] Numerous local and state health agencies have demonstrated in the past decade that rabies can be controlled by a program that includes (1) education of the community about rabies, (2) stray dog control, (3) immunization of resident dogs, and (4) reduction of wildlife reservoirs where they are involved.[13] Education of the community is largely directed at supporting the other essential features of a rabies-control program. Stray dog control requires capable dog wardens, mobile units and a good detention pound with humane euthanasia facilities. No canine immunization program can be successful if there remains at large a sizable stray dog population to maintain a rabies epizoötic.

Successful canine immunization was demonstrated by Pasteur, but his method was impractical for large scale use. Semple developed the first rabies vaccine which could be carried to the field. Japanese veterinarians used this agent with success in the 1920's. It was first used in the United States in Vermont in 1928 with good results. Following this, it gave variable results in the hands of investigators and health authorities. It was not until the Habel mouse protection test was developed that there was any way of measuring the value of the vaccine before it was released. Johnson, Leach and Webster carried on numerous laboratory and field trials with

* To those interested in further information the WHO reports on brucellosis, rabies, and zoönoses are recommended.[7, 8, 9]

rabies vaccination. In 1945 Johnson reported on the efficacy of canine immunization in the control of rabies.[14] Since then there has been an increasing acceptance of this procedure in rabies control, supported by dramatic results. The number of vaccinations has increased from less than 1,000,000 in 1940 to over 3,500,000 in 1950. It is realized that the Semple phenolized tissue vaccine is not an ideal agent, hence considerable time has been devoted to the development of more efficient agents. Among these newer vaccines there are an avianized, ultra-violet attenuated type and a benzene extracted calcium acetate washed type. The adaptation of rabies virus to embryonated eggs was done by Koprowski and Cox with a virus referred to as the Flury strain.[15] Investigations with the avianized living vaccine have revealed that it provides very good protection for a year. Experiments are now under way to determine if the immunity extends beyond one year. The ultra-violet vaccine is under study, as is the benzene extracted calcium acetate washed agent. The latter was developed for human rabies immunization to prevent the postvaccinal paralysis which sometimes follows the use of the usual tissue rabies vaccines. Another new development in the treatment of man and animals following rabies exposure is hyperimmune rabies serum. This product, made from rabbit or sheep blood, is being used to avoid postvaccinal paralysis, especially in persons such as veterinarians and animal handlers who have had previous antirabies vaccination.

In the control of rabies, it is necessary to immunize at least 70 per cent of the resident dog population to prevent new outbreaks of the disease.[16] It should also be realized that not all immunized animals will successfully resist the disease, especially if they are exposed to multiple bites from a rabid animal. Any animal so exposed should be detained for a six month period to be certain that it does not develop disease. The incubation period in dogs is usually 12 to 50 days, but it may extend beyond 200 days. There has been little investigation of treatment of exposed dogs since Pasteur's original report.

The importance of wild animal population reduction and control has been emphasized by the sylvatic outbreaks of rabies in red and gray foxes in eastern and southern United States.[16] The states which are west of the Mississippi Valley have had a troublesome problem with skunks and civet cat rabies. In the West there are occasional reports of rabies in coyotes and wolves. Other animals reported infected are squirrels, opossums, wildcats, mountain lions, etc. The reduction in the number of these animals which are reservoirs is essential to the control of rabies. Reduction is usually done by trapping, shooting or poisoning under the direction of a wildlife management specialist.

The control and eventual eradication of rabies are the primary objectives of veterinary public health activities. If the above outlined program can be effected in the epizoötic areas, the disease will eventually be eliminated. To do this, everyone who is concerned with rabies must convert others to the program.

Q fever is by far the most interesting rickettsial type of animal disease spread to man. This disease is not only of importance to civilian health, but during World War II it was a serious military disease problem in German troops in Greece and Allied troops in Italy.[17] It is a disease of little economic importance, inasmuch as it produces no discernible symptoms in animals and does not interfere with lactation. Cattle, goats and sheep have been found naturally infected in the United States. In addition, the cattle ear tick (*Otobius megnini*), dog tick (*Rhipicephalis sanguineus*) and Rocky Mountain tick (*Dermacentor andersoni*) have been found infected in the West. Outside this country the lists of ticks and animals infected are larger.[18]

The causative organism, *Coxiella burnetii,* is found in the milk,[19] placenta [20] and vaginal discharges of domestic animals. Bell, Beck and Huebner [21] reported on 50,000 human cases that had occurred in Los Angeles over a period of years. They pointed out that individuals who used raw milk had an incidence of disease which was ten-fold higher than consumers of pasteurized milk. The rate of infection also was significantly high among workers at dairies and people whose residences were close to dairy farms. An outbreak of Q fever among a ship's crew was attributed to infected goats that were aboard in transit.[22] Infection associated with sheep has not always been satisfactorily explained.[23] Outbreaks among industrial workers handling sheep and sheep products have been reported.[24] *Coxiella burnetii* is one of the most tenacious organisms that has been studied. It will survive one-half of 1 per cent phenol for 96 hours at 4° C. and some will also survive the usual vat pasteurization temperature of 143° F. for 30 minutes. Investigations of effective control, including pasteurization and animal immunization, are being followed. There is little evidence that blood-sucking arthropods are important in the transmission of the disease among animals or to man, even though they are often found infected. The possibilities of airborne infection are suggested in a study of an institutional outbreak of Q fever.[25]

The control of Q fever is an unanswered problem, but it is realized that certain precautions can be taken. These include (1) pasteurization of dairy products—even though not 100 per cent effective, it destroys large numbers of *C. burnetii;* (2) the restriction of the movement of animals from enzoötic areas to disease-free areas, unless it can be shown that they are disease-free; (3) the use of immunizing agents among laboratory and field investigators who are exposed to high concentrations of the organism. These agents are not so effective as some other vaccines, but they do offer a certain degree of protection. The data that have been collected on the natural history of the disease seem to indicate that the control of the animal disease is important to public health.

Brucellosis is one of the most common animal-to-man diseases in most parts of the world. It is exceeded only by bovine tuberculosis in the British

Isles, Germany and eastern Europe; hydatid disease in Australia, Uruguay, Argentina and the eastern Mediterranean, and perhaps anthrax and leptospirosis in certain other countries. The history of brucellosis or undulant fever is well known. The reported disease has increased steadily in man in the past 25 years in the United States, until recently, when there has been a slight drop. The reported number of human cases has varied between 4,000 and 7,000 in the past decade, but public health authorities concerned with the disease have estimated that there may be more than 10,000 cases annually.[27] The prevalence in cattle as indicated by blood agglutination tests has declined from 14 per cent in 1935 to less than 4 per cent in 1950.[28] The distribution in swine has probably increased in the past decade; however, there are no accurate data to establish this as a fact.

The disease may be transmitted from cows by the ingestion of contaminated milk and milk products, but more often it is from direct contact with the cow that has delivered or aborted. The handling of the calf and the placenta and vaginal discharges are also dangerous types of exposure. Jordan reported in Iowa that the rate of infection was much higher in male farm workers than in females or children on the same premises.[25] Other groups with high rates of infection are veterinarians, packing house employees and rendering plant workers. It has been estimated that between one-half and two-thirds of all human infections can be attributed to occupational hazards.[26, 27]

McCullough, in a study at packing houses in Chicago, recovered *B. abortus, B. suis* and *B. melitensis* from 35 swine out of 5,000 hogs examined.[29] The isolation of the organism is always difficult, and these isolations probably represent only a small number of the infected animals. Most of the swine infection is reported in the Midwest, but the disease is also reported in the southern states. Hutchings, of Purdue University, in a study on meat products processed from diseased hogs, showed that *Brucella suis* could live for more than 20 days in a hog carcass.[30]

The transmission of brucellosis from swine to man is attributed to occupational contact on the farm or in the packing house. Vaginal discharges, aborted pigs and semen of infected boars are highly contaminated sources of brucella. The quantities of semen from the boar are so great (200 to 400 c.c.) that they contaminate the premises.[28] It is known that the brucella may live outside the animal under favorable conditions. Occasionally milk cows become infected with *B. suis* and spread the infection to human populations.[29]

Brucellosis in goats and sheep due to *B. melitensis* has been rare in the United States in recent years but is quite common in Mexico, Argentina, France, Spain, Italy and Malta.[31] The presence of *B. melitensis* in swine and cattle has recently been observed and is difficult to explain.[32, 33] Huddleson has suggested that the infection may have been introduced to the Midwest in cattle from the southwest range or Mexico.[34]

The transmission of *B. melitensis* from goats and sheep to man has been uncommon in the United States, but in Latin America and Europe it is a serious problem. Castaneda is of the opinion that 95 per cent of the human infections in Mexico City are due to contaminated cheese and butter made from goat's milk.[40] The goat also is likely to infect man at the time of parturition or abortion. The animals may be dangerous spreaders for months following abortion or parturition, after which the brucella may localize in regional lymph nodes or in the udder. The contamination of field greens and water supplies with brucella from sheep has been reported as a cause of human disease in France.[7]

Control measures to prevent the spread of disease from animals to man include (1) pasteurization of milk and milk products, including cheese; (2) the testing and removal of infected animals from the herd and, in the case of swine and goats, the sale of the herd for slaughter; (3) the immunization of calves between six and 12 months of age; (4) the strict earmarking of infected animals for slaughter only; (5) proof that animals offered for sale are free of disease and are from a disease-free herd, and (6) education of those who work with animals on how the disease is transmitted to man and what personal hygiene precautions should be followed. Meat inspection is of value in recognizing lesions in swine when present, but usually there is little or no gross pathologic evidence of disease in cattle.

The control of brucellosis as a human disease is dependent upon its eradication in animals. Pasteurization has reduced the prevalence of disease in urban populations, but the incidence of brucellosis in rural and animal handling populations will remain high until bovine and porcine brucellosis are eliminated.

There are other interesting bacterial diseases, such as salmonellosis, which probably has the widest host spectrum of any disease.[41] Salmonella infections are described in poultry, including all types of domestic fowl and many wild birds. Swine have the highest prevalence among slaughtered animals.[42] Dogs have been recognized in recent years as important carriers.[43] Occasionally cattle and horses are reported infected.[44]

Salmonella are usually transmitted to man in food products of animal origin, such as dried chicken egg powder, fresh duck eggs, poultry meat, sausage, head cheese and other ground meat products. An interesting epidemiologic observation about this disease is that it can be transmitted from man to animals as well as from animals to man. Its control is dependent on animal hygiene, personal hygiene and the sanitary processing of foods of animal origin.

The medical and public health importance of fungus diseases is a field that is developing rapidly. Numerous fungus diseases are described in man and animal, but it is difficult to ascertain whether they are all interrelated. One of the fungi thought to be communicable from animals to man is trichophytosis (ringworm), of which there are many species among dif-

ferent animal hosts.[45] It is believed that man can transmit these fungi to animals. It is not uncommon for veterinarians to see lesions on animals similar to those seen in man. Among farmers who handle milk cows, certain types of bovine ringworm may develop on the forehead or head where they lean against the flank of cattle.

Other fungus diseases, such as sporotrichosis, aspergillosis, histoplasmosis and coccidioidomycosis, are found in both man and animals, but no one has shown that they are transmitted from animals to man. It is thought that both man and animals become infected from a common source. When cases are recognized in either species, they can be described as sentinel cases, indicating the disease is present in the area.

The control of ringworm in animals is dependent on good veterinary medical care, zoöhygiene and personal hygiene. These measures will prevent the transmission to man.

There are no important protozoan diseases of higher animals which affect the health of man to any considerable degree in the United States. The transmission of *Balantidium coli* from swine to man has been reported under unusual circumstances.[46] Toxoplasmosis, giardiasis and amebic dysentery are reported in animals, but there is no evidence that they are transmitted to man from animals. In South America, Africa and Asia, Chagas' disease, trypanosomiasis and leishmaniasis are serious diseases of man and animals. With the possible exception of Chagas' disease, which has been reported in the Southwest, these diseases have not been reported in the United States, and fortunately there is little likelihood they can become established here because of the climate and ecology.[47]

There are many helminthic diseases of animals found in man. Fluke infestations of animals in this country do not seem to be important to man's health except the schistosoma infections of birds which cause swimmer's itch in the north central states.[48] In Southeast Asia, *Schistosoma japonicum* is found in dogs, pigs, monkeys, rats and water buffalo calves.[49, 50] These animals may contaminate water courses with their feces, which carry the ova. Most of the human infection is due to contamination of the water by other human carriers, but the animals do contribute to the maintenance of the fluke in nature.

The tapeworms of animals are numerous. The ones found in man in the United States are the rat tapeworms (*Hymenolepis nana* and *H. diminuta*), the beef tapeworm (*Taenia saginata*) and the fish tapeworm (*Diphyllobothrium latum*). None of these is common. Outside this country, one of the dog tapeworms, *Echinococcus granulosus*, which causes hydatid disease in man and animals other than those of the canine family, is one of most important animal diseases found in man. It is a major problem on every continent except North America.[51] Dog control and treatment of infected dogs are essential to control it. Meat inspection and disposal of infected carcasses so as to prevent infection of dogs are necessary.

Trichinosis is reported more often than any other round worm infection in the United States. Trichinosis is stated to be more prevalent in the United States than in any other country of the world.[52] It is a disease which can be brought under control, provided regulations are adopted and enforced to prevent the feeding of raw garbage to swine.[53] The incidence of trichinosis in garbage-fed hogs is between 5 and 10 per cent. In grain-fed hogs it is less than 1 per cent. Most human outbreaks of disease occur among those who eat raw or semi-raw pork products. Quite often family groups become infected following the butchering of hogs and the preparation of homemade sausage. The later is one of the most common ways in which people infect themselves, that is, the custom of tasting the raw pork mixtures to determine if they are correctly spiced. If hygienic precautions, such as cooking pork meat products or avoiding tasting raw pork, were always heeded, they would do much to lower human incidence of the disease.

The ectoparasites of animals that affect man include fleas, mites and ticks. All of these cause considerable irritation and, in some cases, carry diseases such as plague by the rat flea (*Xenopsylla cheopis*), and Rocky Mountain spotted fever by the dog tick (*Dermacentor variabilis*). Rickettsialpox, caused by *Rickettsia akari*, is thought to be transmitted to man by the bite of the mouse mite (*Allodermanyssus sanguineus*). The chicken mite (*Dermanyssus gallinae*) is reported to harbor the virus of Western equine encephalomyelitis. The rat mite (*Liponyssus bacoti*) causes severe skin irritations in man. Some people may also have considerable discomfort from the fleas of domestic animals. Most of these problems can be controlled by good environmental and animal hygiene. The use of insecticides has made life much more comfortable for millions of people.

Many types of clostridium organisms are found in the digestive tract of animals, especially horses. These include *Cl. tetani* and *Cl. botulinum*, which can multiply in the intestinal tract of the host without causing any harm. They are passed out and contaminate the environment. Being a spore-former they may remain viable for an indefinite period of time when they enter a wound or food, where they can become toxin producers under certain conditions. The use of tetanus toxoid has reduced the incidence of disease in animals and man. Botulism is not uncommon in animals but rare in man. The outstanding advances in food technology in the past 30 years have made the disease almost unknown.[10]

The second group of diseases, mentioned earlier, were those that do not produce disease in man. They are in many instances host-specific. They include hog cholera, a generalized virus disease of swine only; rinderpest, a generalized virus disease of cattle and closely related herbivora; dourine, a protozoan venereal infection of horses; Johne's disease, or paratuberculosis, caused by an acid-fast organism that produces in cattle a chronic, debilitating gastrointestinal infection; blackleg, a gas gangrene of cattle caused by *Clostridium chauvei;* anaplasmosis, an arthropod-borne protozoan

disease which is one of the most serious cattle diseases of the tropics and semitropics, and contagious pleuropneumonia, a virus infection of cattle which, incidentally, was the first animal disease eradicated in the United States.

In this group there are also animal diseases with names indicating that they may be related to human disease, but no one has demonstrated any relationship. They include calf diphtheria, which has symptoms similar to the human disease but is caused by *Actinomyces necrophorus;* fowl diphtheria, due to a virus; equine influenza, a virus disease with no relation to any other influenza viruses; canine infectious hepatitis; fox encephalitis, and dog typhus.[58-59]

All of these diseases are important to man's welfare and health because of their economic effect and of the loss of necessary animal power and products, as illustrated in the following events. In 1946–47, rinderpest broke out in an epizoötic form in Southeast Asia. The disease of water buffalo and cattle was so widespread as to prevent the harvesting of the rice crops. The result was a shortage of food with far reaching political effects. The outbreak of foot-and-mouth disease in Mexico four years ago has cost our Government over $100,000,000, and the Mexican Government an equivalent amount. In addition, we have lost an important source of 600,000 head of feeder cattle, which were normally imported from Mexico annually. The vast meat resources of Uruguay and Argentina cannot be used in the United States because of the danger of the importation of foot-and-mouth disease. In Central Africa there is an area of 4,000,000 square miles, one-third larger than our country, which would be a wonderful range country for livestock if it were free of trypanosomiasis, which affects animals and man. This area could probably produce most of the animal protein needs of Europe, Africa and a part of Asia. Assistance in the development of these areas can contribute to the improved health and economic standards of the world. Veterinary medical aid has been sent to countries that have requested it under the Economic Coöperation Administration. Similar assistance is being extended under the Point Four Program and through the World Health Organization, Food and Agriculture Organization and the Pan-American Sanitary Bureau.

The last category of zoönoses, mentioned earlier, was that which bridges the first and second categories. They fall into a class of diseases found only occasionally in man, but, as Burnet points out, they may be examples of disease agents that are adapting themselves to higher forms of life.[5] They include diseases such as Newcastle disease, or avian pneumoencephalitis, which is rarely reported in man, or foot-and-mouth disease, which the earlier medical literature reported quite often in man but today is rarely seen; few cases are ever confirmed. Sheep encephalomyelitis (or louping ill), vesicular stomatitis, Aujeszky's disease (or pseudorabies) and infectious equine anemia are others. Swine influenza is one which seems to have a definite

serologic relation to human disease, but there is little epidemiologic evidence to associate it to influenza in man. All of these are similar in that they are virus diseases. Among the more highly developed animal disease agents, such as bacteria and protozoan and helminthic parasites, are numerous agents which are only occasionally reported in man. *Listeria monocytogenes*, a bacterial encephalitis of sheep and cattle, is an example. Among the parasitic diseases there are the Toxoplasma sp., Endamoeba sp., and Schistosomas of animals, birds and various round worms.

In closing, it is well to point out that many of the animal diseases may be used aggressively in warfare. In World War I the French accused the Germans of introducing glanders among their military horses. During World War II there was considerable activity in the investigation of its potentiality. In reading Rosebury's preliminary report to the National Research Council, one is impressed by the large number of animal disease agents that are adaptable to biologic warfare.[60] Many of the agents discussed could be used against both man and animals. Some of these are described as being air-borne infections. There is considerable information to support this hypothesis.[61, 62] Some of it has appeared after retrospective examination of earlier epidemiologic reports.[63] In a more recent publication, Rosebury points out the possibilities of biologic warfare and discusses a number of agents, most of which are the causes of animal diseases communicable to man. They include brucellosis, glanders, psittacosis, equine encephalomyelitis, anthrax and tularemia.[64]

Biologic warfare is no longer a theory but a real possibility that can be effected against man and animals.[65] In either case, early recognition of the disease in man or animals will be of the utmost importance. Research is under way to develop faster methods of virus and bacteria recognition, but until these methods are available the first indication of disease introduction may be the symptoms observed in the higher mammalian species, including man.

The control of animal diseases communicable to man in peace or war requires the coöperation of the physician, the veterinarian, the public health departments, the animal health agencies and the public information services. The physician who makes the diagnosis must report the case and supply the medical history to the epidemiologists who investigate the disease to determine its origin. Often he is assisted by a public health veterinarian who is interested in the epizoötiology of the disease in animals and the possible involvement of contaminated food products of animal origin. After the animal source of the disease is identified, public health or animal disease control measures are put into effect. In many cases the services of other public health or biologic sciences are necessary, especially if there is a problem of water- or arthropod-borne diseases.

Human medicine, veterinary medicine and the public health and biologic sciences have all made significant contributions to the advancement of the

health and welfare of man. They will no doubt continue to do so in the future, but their efforts and contributions will be even greater if they all have closer relations. Your President, Dr. William Middleton, pointed out the need for closer relations between our respective branches of medicine in his invitation to have me appear before the College. I wish to implement his statement further by suggesting that joint meetings of physicians and veterinarians take place in local and state areas. The exchange of information in fields of mutual interest, such as the infectious diseases of animals transmissible to man and other phases of practice and research, will benefit all.

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AIR TRANSPORTATION OF CARDIAC AND PULMONARY PATIENTS*

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AIR transportation of patients has become commonplace. In quickly transporting the sick and wounded from distant areas of military operations, such as Korea, to well-equipped and well-staffed medical facilities which provide thorough, definitive treatment, the airplane is of the greatest value and has been acclaimed by many as one of the really great advances in military medicine.

This paper presents the findings of an investigation carried out by the United States Air Force Medical Service in the worldwide air evacuation system which has been in operation since 1942. An analysis has been made of 1,777 flights of patients with cardiac and pulmonary disorders. They were flown by the Military Air Transport Service during 1949. Only nonpressurized aircraft were used, and 96.5 per cent of the flights were below 10,000 feet.

We have confined this study to disorders of the heart and lungs because these two systems are most likely to be affected by flight. The effects of flight on circulation and respiration in normal individuals have been thoroughly discussed in the literature. There have been several studies of the effects of air transportation on clinical disorders, the first by Tillisch, Stotler and Lovelace,[1] and the most recent by Strickland and Rafferty.[2]

METHODS

Some of the patients were transported by air more than once. These we have considered as separate "patient flights." Graduate nurses aboard the planes recorded the hospital diagnosis and made careful reports of whatever symptoms the patient developed during the flight. Their reports also included any treatment necessary during flight and an estimate of its effectiveness.

In this study we have analyzed these flights of cardiac and pulmonary patients and classified the symptoms reported. (See table 1.) Those unrelated to the patient's disease included symptoms of motion sickness and symptoms due to changes in barometric pressure that would occur in normal individuals (such as block of the Eustachian tube). The symptoms which we considered to be related to the pathologic condition were those concern-

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ing the circulatory and respiratory systems, namely, dyspnea, cyanosis and pain in the chest. Headache and dizziness were considered related when occurring in the group of hypertensive patients.

Cardiac Disorders

There have been many warnings about permitting cardiac patients to fly, in particular those who have coronary disease. The basis for most of these opinions [3, 4] has been the electrocardiographic changes which occur under conditions of hypoxia (oxygen want). In a recent article, May [5] disagrees with the view that electrocardiographic changes are a measure of the ability of the individual to withstand hypoxia. May points out that, in the anoxemia test, the patient is suddenly elevated to a simulated altitude of 18,600 ft. by breathing 10 per cent oxygen. This is a far more severe test of the heart than an airplane ascent, since the plane must climb slowly, allowing time for coronary dilatation and compensation for hypoxia.

Table I

Classification of Reported Symptoms

Unrelated	Related
(a) Motion Sickness	Respiratory difficulty
Pallor	Air hunger
Sweating	Cyanosis
Mild gastrointestinal upset	Chest pain
Nausea	Chills
Vomiting	Headache (in hypertensive)
(b) Due to Altitude	Dizziness (in hypertensive)
Intestinal gas	
Earache	
Toothache	
(c) Miscellaneous	
Nervous tremors	
"Weak and tired"	

The really important consideration in flight is the oxygen supply of the myocardium, which depends upon the coronary circulation but also upon the oxygen saturation of the blood. Most commercial and military evacuation flights are carried out at cabin altitudes below 10,000 feet. At these levels, oxygen saturation of the blood remains above the safe level (over 90 per cent). Above 15,000 feet, oxygen saturation falls off rapidly, so that no amount of coronary dilatation could provide a sufficient oxygen supply to the myocardium. Graybiel [6] reported in 1941 that congestive failure and angina pectoris have been produced in patients with heart disease on exposure to altitudes between 14,000 and 20,000 feet without oxygen. For this reason, cardiac patients should not be exposed to altitudes above 10,000 feet without oxygen. As a practical matter, Friedberg [7] states that most patients with angina pectoris tolerate flights at moderate altitudes without untoward symptoms.

TABLE II

Incidence and Analysis of Symptoms Reported during 464 Flights of Patients

Total Flights	Number without Symptoms	Number with Symptoms	Type of Heart Disease	Analysis of Symptoms						
				Unrelated			Related			
				Motion Sick	Earache	Apprehension	Cyanosis	Precordial Pain	Headache	Dizziness
12	12	0	Angina pectoris							
37	36	1	Myocardial infarction (healed)					1*		
5	4	1	Arteriosclerotic heart disease (unspecified)	1						
60	50	10	Essential hypertension	7	1				1	1
9	8	1	Malignant hypertension		1					
73	70	3	Hypertension c cardiac dis.†	3						
132	126	6	Rheumatic fever							
			Acute (45)	1		1				
			Chronic (7)	1						
			Unspecified (80)	2	1					
28	27	1	Rheumatic fever c carditis	1						
3	2	1	Chorea c carditis	1						
25	24	1	Rheumatic heart disease, chronic†	1						
6	5	1	Congenital				1*			
19	18	1	Arrhythmias	1						
9	9	0	Pericarditis, chronic							
9	9	0	Myocarditis							
			Acute (2)							
			Chronic (7)							
1	1	0	Bact. endocarditis, acute							
2	1	1	Bact. endocarditis, subacute	1						
2	2	0	Aortic insufficiency							
8	8	0	Valvular disorders							
5	5	0	Cardiac enlargement or hypertrophy							
19	19	0	Unspecified heart disease†							
				20	3	1	1	1	1	1
464	436	28		24			4			

* Also had respiratory difficulty.
† Compensated.

There were 464 reports on flights of patients with heart disease.* (See table 2.) It was somewhat surprising that 49 patients with coronary heart disease were flown. As at this time (January to October, 1949), the military service prohibited air transportation of coronary cases until 60 days

* Only 10 flights were above 10,000 feet, and no related symptoms were reported on these flights. One may consider that the entire group of cardiac patients flew below 10,000 feet.

following the last attack, all of these cases were chronic. None of the 12 with a diagnosis of angina pectoris had any symptoms during flight. One of the patients with healed myocardial infarction, a 42 year old officer, developed respiratory difficulty and slight precordial pain which were easily relieved after oxygen administration.

There were 60 cases of essential hypertension without known cardiac involvement. Two of these had related symptoms. One experienced headache which was relieved on lying down, and the other, a 19 year old boy, developed dizziness. There were nine with a diagnosis of malignant hypertension. One of these developed an ear block on descent which, of course, was not related to his condition. There were 73 hypertensives who had established cardiac lesions. It is presumed that they were compensated at the time of the flight.

Among the 31 rheumatic patients with known cardiac involvement were 28 cases of acute rheumatic fever and three patients with chorea. One hundred thirty-two cases were diagnosed rheumatic fever. Because of the extremely high incidence of carditis in rheumatic fever, we have included these patients in the study although there was no mention of heart disease in their diagnosis. None of this group had any related symptoms. Seven were motion sick and one had earache and another apprehension.

The congenital group is small; of the six cases, the one child who developed related symptoms was cyanotic on the ground before the flight and became more cyanotic and somewhat dyspneic during the flight. He responded to oxygen administration.

Cardiac arrhythmias were not affected by flight. Nine cases of myocarditis had no symptoms, nor did nine cases of pericarditis. One of the three cases with bacterial endocarditis became motion sick but had no other complaint. There were 10 patients with valvular disorders, five with cardiac enlargement and 19 with unspecified cardiac abnormalities. No one in these groups had any complaints.

Pulmonary Disorders (Non-tuberculous)

Pulmonary disturbances which require special consideration in air transportation are atelectasis or pneumothorax, severe bronchial asthma and febrile diseases, such as pneumonia, which may produce severe toxicity.

In pneumothorax, the gases entrapped in the pleural space will expand with ascent. Tillisch [4] showed that at 10,000 feet the volume will equal one and one-half times sea-level volume. This expansion may or may not cause respiratory distress. A partial pneumothorax expanding 50 per cent may produce no symptoms. On the other hand, one death has been reported by Dowd [5] as a result of flying a patient with pneumothorax at 16,000 feet. Recent spontaneous pneumothorax has been feared because of the theoretic possibility of a flap valve's opening from the bronchus to the pleura so that air could easily enter but could not get out of the pleural space, resulting in

a tension pneumothorax. This "armchair" reasoning has prevented the air transportation of many cases of spontaneous pneumothorax.

There were 568 flights of patients with nontuberculous pulmonary disorders. (See table 3.)

TABLE III

Nontuberculous Pulmonary Disorders: Analysis of In-Flight Symptoms in 568 Flights

Total Flights	Number without Symptoms	Number with Symptoms	Type of Disease	Unrelated					Related		
				Motion Sick	Headache	Earache	Toothache	Other	Asthma Attack	Chest Pain	Respiratory Difficulty
19	18	1	Pneumothorax (spontaneous)	1							
13	12	1	Atelectasis (one lobe)	1							
3	3	0	Atelectasis (unspecified)								
215	202	13	Asthma, bronchial	3			1	3*	3	1	2
4	3	1	Tumor, mediastinum	1							
15	12	3	Tumor, bronchus		1						2
14	14	0	Tumor, lung parenchyma								
4	4	0	Tumor, pleura (endothelioma)								
27	24	3	Pneumonia, acute	1		1					1†
21	18	3	Lung abscess		1					2	
49	45	4	Pleurisy, acute (non-tbc.)	2			1				1
31	28	3	Pleurisy, chronic (non-tbc.)	3							
15	13	2	Pleurisy, c effusion (non-tbc.)	2							
8	7	1	Empyema, acute (non-tbc.)							1	
31	27	4	Bronchitis, chronic	2			2				
77	33	6	Bronchiectasis, one lobe (39)	2		2		1			1
	4	0	Bilateral (4)								
	32	2	Unspecified (34)	2							
2	2	0	Pneumoconiosis								
2	0	2	Mycosis, lung	1	1						
1	1	0	Sarcoidosis, lung								
5	5	0	Hemothorax (traumatic)								
3	2	1	Pulmonary hemorrhage	1							
9	8	1	Undiagnosed pulmonary disease	1							
				23	3	3	4	4	3	4	7
568	517	51		37					14		

* 2 dizzy (over 10,000 ft.); 1 sweating.
† Chill.

Of the 19 cases of spontaneous pneumothorax, not one had any symptoms related to his condition.

There were 16 cases of atelectasis, including one patient who had a massive collapse of a lung. None of these had any respiratory symptoms in flight.

There were 215 cases of bronchial asthma. Seven had unrelated complaints. Three of the six with related complaints had a frank attack of

asthma and two had some respiratory difficulty. Another had mild pain in the chest. Two and eight-tenths per cent of the 215 asthma patients had symptoms referable to the disorder.

Thoracic neoplasms included four tumors of the mediastinum and four tumors of the pleura, with varying degrees of pleural effusion. There were 29 lung tumors. Two of 15 cases of bronchogenic carcinoma experienced mild respiratory difficulty, presumably on the basis of blocking of the airway. Both of these patients were relieved with oxygen administration.

There were 27 cases of pneumonia. One of these, a 22 year old man, developed related symptoms. He had suffered extensive second- and third-degree burns and had developed pneumonia subsequent to the burns. During flight he showed pallor and complained of stomachache and developed a mild chill and some dyspnea.

Two of 21 patients with lung abscess developed pain in the chest which required simple medication. These patients are usually watched closely for coughing and vomiting because of the possibility that infective material might be spread to a noninvolved area of the lung by retching.

Pleural effusion is not a serious problem, since fluid in the pleural space does not expand; hence the amount of respiratory embarrassment will not be increased by ascent to altitude. Of course, a large collection of fluid with respiratory embarrassment on the ground requires removal of the fluid before flight.

The 95 cases of pleurisy included 49 cases of simple pleurisy without effusion, 31 cases of chronic pleurisy and 15 cases of pleurisy with effusion. One patient with related symptoms was a 41 year old sergeant seriously ill with an acute pleurisy. He became airsick, was nauseated and vomited, and experienced respiratory difficulty at an altitude of 9,000 feet. His dyspnea was not relieved by descent to 7,000 feet but did respond to oxygen, and the flight was completed successfully.

There were eight cases of nontuberculous empyema. All of these patients were very ill. A 24 year old woman with a left empyema complained of pain and tightness in the chest at an altitude of about 10,000 feet. She developed some cyanosis and was relieved by oxygen.

Of 77 patients with bronchiectasis, one developed related symptoms. He was an 18 year old boy with severe bronchiectasis of the left lower lobe. He showed severe apprehension before the flight and was nervous during the ascent. At 2,500 feet he complained of respiratory difficulty. It is very unlikely that this was due to the ascent, because the pressure differences from sea level to 2,500 feet are hardly sufficient to account for respiratory difficulty.

Miscellaneous pulmonary diseases include two cases of pneumoconiosis, two cases of fungus disease of the lung, one case of sarcoidosis and nine undiagnosed pulmonary diseases. None of these patients had any related complaints.

Pulmonary Tuberculosis

Patients with pulmonary tuberculosis ordinarily can be transported by air, but a minor percentage require special consideration. Roper and Waring [9] have reported a study of possible later effects of air transportation of patients with tuberculosis. They followed a series of 143 patients for periods of up to four years after they had been flown. The flight had little or no effect upon the subsequent course of the tuberculosis in their series of cases. Two deaths occurred out of 143 patients, one seven months and the other 27 months following air evacuation. One cannot conclude that the flight produced this effect, or, if such a judgment is made, then one must

Table IV

Pulmonary Tuberculosis: Analysis of In-Flight Symptoms in 745 Flights

Total Flights	Number without Symptoms	Number with Symptoms	Type of Disease	Analysis of In-Flight Symptoms					
				Unrelated		Related to Tbc.			
				Motion Sick	Other	Resp. Difficulty	Cyanosis	Chest Pain	Hemoptysis
560	515	45	Pulmonary tbc.	21	13	4	5*	2	
75	66	9	Obs. for pulmonary tbc.	7	2				
43	38	5	Pulmonary tbc. moderately advanced	2	1	1*		1	
41	39	2	Pulmonary tbc. far advanced			2			
3	1	2	Pulmonary tbc. c̄ hemorrhage		1				1
7	5	2	Pulmonary tbc. c̄ pneumothorax			1		1	
11	10	1	Pulmonary tbc. c̄ effusion			1*			
5	4	1	Pulmonary tbc. c̄ empyema			1*			
				30	17	10	5	4	1
745	678	67		47		20 (2.7%)			

* Over 10,000 feet.

also assume that the 89.5 per cent of the patients who improved following the flight did so because of the flight.

There were 745 flights of patients with tuberculosis. (See table 4.) There were 560 reports with a diagnosis of pulmonary tuberculosis without further qualification. While it would be desirable to separate tuberculous patients into minimal, moderately advanced and far advanced, we are unable to make this distinction except where the specific diagnosis was noted on the report. Of the total of 560, 11 had related symptoms. Four had some dyspnea. All five patients who developed cyanosis were flying above 10,000 feet. One man complained of pain in the chest just before landing. Another patient was acutely ill, with evidence of toxemia and a paroxysmal cough. He complained of pain in the chest during flight.

Another group of 75 reports listed the diagnosis of "observation for pulmonary tuberculosis." This conforms to military practice; the diagnosis is not made without the demonstration of the tubercle bacilli. It cannot be stated how many of these patients actually had pulmonary tuberculosis. The presumption is, however, that a great majority of them had minimal disease. None of the group had related symptoms.

There were 43 patients who were diagnosed as moderately advanced. Two of these had related symptoms. One who had a temperature of 103° F. before flight developed mild respiratory difficulty above 10,000 feet. The other complained of pain in the chest on landing. The latter patient was an emotionally unstable individual who was greatly upset, and it was difficult to interpret this pain.

TABLE V

Pulmonary Tuberculosis: Effect of Ascent over 10,000 Feet Altitude on the Incidence of Symptoms during Flight

Total Number Flights	Number without Symptoms	Number with Symptoms	Type of Disease	Altitude Flown	Unrelated				Related		
					Motion Sickness	Other: Pallor Sweat	Other: Headache	Other: Weak Tired	Respiratory Difficulty	Chest Pain	Cyanosis
423	390	33	Pulmonary tbc.	Below 10,000	(4.5) 18 (4.3)	4	4	1	4	2	0
69	57	12		Above 10,000	3	3	1				5
68	68	0		Unknown							
					21	7	5	1	4	2	5
560	515	45			34				11		
66	57	9	Obs. for pul. tbc.	Below 10,000	7	1	1				
5	5	0		Above 10,000							
4	4	0		Unknown							
					7	1	1				
75	66	9			9						
29	26	3	Pul. tbc. moderately advanced	Below 10,000	2		1		1	1	
4	2	2		Above 10,000							
10	10	0		Unknown							
					2		1		1	1	
43	38	5			3				2		
34	32	2	Pul. tbc. far advanced	Below 10,000					2		
2	2	0		Above 10,000							
5	5	0		Unknown							
									2		
41	39	2							2		

TABLE V—*Continued*

Total Number Flights	Number without Symptoms	Number with Symptoms	Type of Disease	Altitude Flown	Unrelated				Related		
					Motion Sickness	Pallor Sweat	Headache	"Gas"	Respiratory Difficulty	Chest Pain	Hemoptysis
2	1	1	Pul. tbc. c̄ hemorrhage	Below 10,000				1			1
1	0	1		Above 10,000							
								1			1
3	1	2			1				1		
7	5	2	Pul. tbc. c̄ pneumothorax	Below 10,000					1	1	
0	0	0		Above 10,000							
									1	1	
7	5	2								2	
9	9	0	Pul. tbc. c̄ pleural effusion	Below 10,000					1		
2	1	1		Above 10,000							
									1		
11	10	1								1	
4	4	0	Pul. tbc. c̄ empyema	Below 10,000					1		
1	0	1		Above 10,000							
									1		
5	4	1								1	
574	524	50	Total	Below 10,000	(8.7%)						
84	67	17		Above 10,000	(20.2%)						
87	87	0		Unknown							
745	678	67			(9.0%)						

There were 41 cases diagnosed as far advanced pulmonary tuberculosis. Several of these were in serious condition at the time of their flight. Two showed related symptoms. One developed respiratory difficulty and air hunger which responded to oxygen. The other patient with dyspnea was a man with multiple cavities, who was on the seriously ill list at the time of the flight.

Three patients with pulmonary tuberculosis had experienced a pulmonary hemorrhage shortly before the flight was undertaken. Renewal of the bleeding occurred in one of the three patients. He became motion sick and, as a result of vomiting three times during a one hour flight, brought up 200 c.c. of blood. Perhaps the motion sickness contributed to his hemoptysis.

There were seven cases of pulmonary tuberculosis with pneumothorax. This presents a picture different from spontaneous pneumothorax. Two

of the tuberculous cases had related symptoms, whereas none of the 19 cases of spontaneous pneumothorax had any complaints. One of the tuberculous cases had already suffered complete collapse of one lung and was seriously ill. He developed respiratory difficulty which was relieved with oxygen. The other had a tuberculous abscess of the right lung with a complication of pyopneumothorax on that side. He developed moderate thoracic pain which readily responded to simple analgesics and oxygen administration.

There were 11 cases of tuberculosis with pulmonary effusion and five of tuberculosis with empyema. Two of the 16 had respiratory difficulty above 10,000 feet.

The question of the effect of altitude on the development of in-flight symptoms was discussed by Roper and Waring.[9] We have divided our cases into those who flew above 10,000 feet and those who flew below that altitude. (See table 5.) Symptoms were reported in 8.7 per cent of 574 cases in flight below 10,000 feet. On the other hand, symptoms were reported in 20.2 per cent of 84 patients who flew above 10,000 feet.

Summary

The symptoms were reported in the group of 1,777 flights of patients with cardiac and pulmonary disorders. In 464 flights of patients with cardiac disease, four had related symptoms, an incidence of less than 1 per cent. None of the symptoms was severe, and none would contraindicate future air transportation of such patients. There were 568 flights of patients with pulmonary disorders other than tuberculosis, 2.4 per cent of whom had mild symptoms related to their disorder. There were 745 flights of patients with pulmonary tuberculosis and its complications, 2.7 per cent of whom exhibited mild or moderate symptoms related to their disorder. There was no death in the total series. All of the flights were completed successfully.

Conclusions

We have not observed any contraindications to the air transportation of cardiac or pulmonary cases in these flights below 10,000 feet. Moribund patients should not be transported by air or by any other means, and it is apparent that patients with certain cardiac disorders and with respiratory embarrassment will require oxygen therapy and experienced flight attendants. Whether an individual patient should be transported by air or not depends upon his condition, the altitude to be flown, the availability of oxygen and the qualifications of the flight attendants. In general, however, a patient who can be transported at all can be flown below 10,000 feet.

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THE ENCEPHALOPATHY OF HYPERINSULINISM *

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Hyperinsulinism, in this discussion, is defined as the state produced by excessive amounts of insulin in the body, whether the insulin is exogenous or endogenous in origin. Although the term has been widely used since it was first proposed by Harris in 1924 [1] as indicative of the clinical state produced by excessive *endogenous* (spontaneous) sources of insulin, as in hypertrophy, neoplasm or functional oversecretion of the islets of Langerhans, the far more frequent occurrence of the inadvertent administration of overdoses of insulin lays greater claim to the usage and application of a name so descriptively clear in its semantics. The general adoption of this term, in the light of its broader meaning, would eliminate such unfounded, inaccurate and partially descriptive labels as "insulin shock," "insulin reaction," "insulin coma" and hypoglycemic "shock," "reaction" or "coma."

The term "shock" is now applied to practically all conditions of acute peripheral circulatory collapse.[2] This state is rarely encountered, except terminally, as a manifestation of hyperinsulinism. Its popular use in this connection is therefore misleading and should be condemned. If used in the sense of a sudden severe stress to the organism, as in electric shock therapy, there still remains confusion with the shock syndrome of collapse. Coma is present during only one period of the multiphasic syndrome of hyperinsulinism which often presents cerebral manifestations not only before actual coma is reached, but also after consciousness has returned. Although coma is an outstanding symptom of hyperinsulinism, it is a part which should not be mistaken for the whole. Terms which include "coma," therefore, are not sufficiently inclusive unless the reference is specifically to that phase of hyperinsulinism.

For many years an occasional lack of correlation between the clinical and laboratory observations in hyperinsulinism has been noted.[3, 4, 5] The characteristic clinical symptoms may occur in the presence of normal or elevated levels of glucose in the blood, or may be absent in the presence of severely depressed levels. From these observations it is obvious that the utilization of glucose by the brain cannot be measured by the actual amount supplied to it (i.e., the amount of glucose in the blood stream). Despite an adequate supply (normal or elevated levels of glucose), there may be a lack of availability of glucose to the brain cells because of an impairment of the mechanism of transference of glucose from blood to tissue. Other possible explanations are an inability of the cells to absorb adequate amounts

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of glucose transferred to them, or to utilize it properly on delivery.[3] Although a state of cerebral *glycopenia* may be a large factor in the pathogenesis of the disturbed cerebral cellular metabolism which results, it appears then that hypoglycemia is not the only altered physiologic state concerned. Consequently, to label this condition as "hypoglycemic" is to ignore the fact that on occasion hypoglycemia need not be present, and that possibly another factor must be present, at least in hyperinsulinism which is severe enough to produce permanent encephalopathy. Further discussion of this will be undertaken later.

The variability and multiplicity of symptoms seen in hyperinsulinism are well known. These characteristics of the condition appear to be related to the size of the initiating dose of insulin, the inherent variability in response to insulin of the individual, the widespread areas of the brain which may be affected and the particular phase eventually reached. All the symptoms appear to be encephalopathic in origin. Usually they make their appearance in a definite sequence, and on that basis have been divided by Himwich [8] into five groups or phases:

1. Cortical Phase—depression of cortical functions.
2. Diencephalic Phase—freeing of subcortical motor nuclei from cortical regulation.
3. Mesencephalic Phase—midbrain liberation.
4. Premyelencephalic Phase—resembles decerebrate rigidity (brain sectioned through the mesencephalon).
5. Myelencephalic Phase.

In the precoma or cortical phase, many of the following symptoms may be seen: trembling, tenseness, cardiac palpitation, hunger, weakness, perspiration, mental retardation, emotional instability, headache, nausea, areas of numbness, diplopia, wild excitement, mania, somnolence and disorientation. The symptoms noted in the early stages of coma are: muscle twitchings, spasms, convulsions, primitive movements (involuntary sucking and grasping, elicited by placing an object in the hand or between the lips), motor restlessness, hissing, snarling, grimacing, hyperirritability. As coma deepens, rigidity is characteristically observed, the Babinski response is positive and extensor spasms occur. This stage resembles decerebrate rigidity as severe opisthotonos may be present. In deepest coma are noted shallow respirations, bradycardia, pallor, complete flaccidity, low temperature, pinpoint pupils, absent deep reflexes and absent corneal reflex.

If the hypoglycemia is alleviated, the injury to the brain may prove of short duration and reversible, or, despite the attainment of hyperglycemia, it may prove to be irreversible. In the latter instance, the permanent results of encephalopathy may be hemiparesis, ataxia, incontinence, aphasia, choreiform movements, Parkinsonism, epilepsy, mental deterioration or idiocy.

Not infrequently the encephalopathy is so extensive that coma persists and death ensues in from three to 20 or more days.[6]

Many believe that evidence of permanent damage to the central nervous system is encountered with relative rarity, considering the large number of diabetic persons who are treated daily with insulin.[7] There are no available statistics relative to the incidence of even obvious instances of permanent encephalopathy produced by hyperinsulinism in the course of the treatment of diabetes mellitus. The incidence of such untoward results in the Sakel method of inducing the early coma phase of hyperinsulinism in the treatment of psychoses ("shock therapy") has been variously reported to be from 3 per cent to 30 per cent.[8] Obviously this deliberate production of a more than moderate degree of hyperinsulinism would produce a higher incidence of cerebral damage than the inadvertent administration of overdoses of insulin. Statistics, were they available, would undoubtedly vary with the locality, and the education and intelligence of the persons under treatment. In our experience, instances of severe hyperinsulinism have been encountered more frequently, perhaps, than in the experience of many. This is probably due to the more frequent occurrence of apathy, ignorance, alcoholic addiction and personality defects among the diabetic persons of a large, poverty-stricken area.

The following case records are illustrative of the encephalopathy produced by severe hyperinsulinism: in case 1, a change in personality resulted; in case 2, mental deterioration, partial paralysis and aphasia; in cases 3 and 4, death. In addition, a fifth case (case 5), reported in detail previously,[9] in which encephalopathy appeared to be considerable but in which apparently complete recovery occurred, is included.

Case Reports

Case 1. A 31 year old woman entered the hospital in coma at 4:30 p.m., September 15, 1949. The history was furnished by the patient's sister. Shortly before admission she had been found unconscious, perspiring freely and breathing in a noisy manner. The patient was known to have had diabetes mellitus for 10 years. At 1:00 p.m. on the day of admission she had received 60 units of protamine zinc insulin and, possibly, some regular insulin in addition.

Initial examination disclosed a Negro woman in coma. The skin was cold and moist, respirations rapid and shallow, pupils dilated, equal and reacting promptly to light. The blood pressure was 110 mm. Hg systolic and 80 mm. diastolic. The heart sounds were normal, the rhythm was regular and the rate 92 per minute. There was no abnormal reflex or paralysis. During the examination, muscle twitchings in the arms and legs were noted. The urine on admission contained no sugar, acetone or albumin.

The patient was given 50 c.c. of 50 per cent glucose intravenously, followed by 1,000 c.c. of 10 per cent glucose in distilled water. During this therapy, light convulsions ceased and coma appeared to decrease as the patient became more restless and cried out at intervals. After several hours occasional traces of sugar were found in the urine, but approximately 18 hours after admission the blood sugar was reported to be "below 50 mg. per 100 c.c.," and the carbon dioxide combining power was 48

vol. per 100 c.c. The patient remained in coma for more than 24 hours after its onset. When consciousness returned she appeared lethargic, irrational and completely disoriented. Lumbar puncture on September 21 was productive of normal findings: initial pressure, 80 mm. H_2O; crystal clear spinal fluid; no cell found. The abnormal mental state persisted unchanged for the next 10 days. During this period, despite the attainment of consciousness, the patient was totally incontinent of urine and feces. When insulin was given occasionally because of recurrent mild acidosis, it was noted that the fall of the blood sugar level was greater than expected. Difficulty was encountered in controlling the diabetes because of unusually rapid swings from hypoglycemia to mild acidosis. On the ninth hospital day, slight left facial weakness and diminished left abdominal reflexes were discovered. Eleven days after admission the patient became completely clear mentally and continent. She now exhibited amnesia for all the recent past events. For the remainder of her hospital stay, the patient, although rational, appeared to be withdrawn and melancholic. At times she would fly into a rage without provocation. This personality change was present at the time of discharge on October 15, 1949, one month after admission.

Comment: Although the duration of coma in this case was not much more than 24 hours, considerable derangement of the mental processes persisted for 11 days. Incontinence, not an infrequent occurrence in hyperinsulinism, appeared to be unusual in degree and duration. In a group of disturbed patients with acute psychogenic psychoses, incontinence was reported to be a frequent symptom (20 to 30 per cent), particularly in dementia precox of the catatonic type and manic depression in the manic phase.[10] Even after considerable improvement had occurred in 11 days, this patient's behavior at times was suggestive of a psychosis. The sequelae of hyperinsulinism may mimic the inorganic psychoses.

Case 2. A 48 year old woman entered the hospital in coma at 7:00 p.m. on May 8, 1950. The history, later obtained from the husband, was that the patient had apparently fallen asleep earlier that day while sitting in a chair. Several hours later she began to perspire freely and to "foam at the mouth." Since he could not arouse her, he summoned an ambulance. The patient was known to have had diabetes mellitus for about nine or 10 years. Recently she had been taking 60 units of protamine zinc insulin daily. In September, 1948, she had been treated at this hospital for diabetic acidosis. Since then she had complained of frequent dizzy spells, headaches and blurring of vision, especially in the evenings and early mornings. Four months before the present admission, during one of these episodes of vertigo, she fell and struck her head. The blow resulted in unconsciousness of unknown duration. Except for the addition of posterior nuchal pain, no alteration of symptoms was noted following this incident.

Examination disclosed a well developed, fairly well nourished Negro woman in deep coma. The skin was cold and moist, and the respirations were stertorous. Spasticity of the extremities was present, and occasional generalized clonic contractions were seen. The blood pressure was 110 mm. Hg systolic, 70 mm. diastolic; cardiac rhythm was regular, rate 96 per minute, and the heart sounds were of good quality. No murmur was heard. The deep reflexes were diminished and equal bilaterally. There was no motor weakness or sensory disturbance. The urine contained neither sugar nor acetone.

The patient was given 100 c.c. of 50 per cent glucose, followed by an intravenous infusion of 10 per cent glucose in distilled water. Coma appeared to diminish somewhat, but consciousness did not return. Lumbar puncture yielded crystal clear spinal

fluid under a pressure of 230 mm. of water. No cell was found. The blood sugar (after parenteral glucose) was 54 mg. per 100 c.c.; CO_2 combining power, 62 vol. per 100 c.c.

The following morning deep coma was still present. The blood pressure was 150 mm. Hg systolic, 80 mm. diastolic; temperature, 102.2° F. Rhonchi were heard over both lung fields. The pupils were pinpoint. The extremities were spastic, with the upper extremities held in flexion and the lower in extension. The deep reflexes were hyperactive and equal bilaterally. The Babinski reflex was positive bilaterally. No change in the patient's condition was noted despite the intermittent use of parenteral glucose solutions. Glycosuria appeared during glucose administration but rapidly disappeared when this was interrupted. By afternoon the blood sugar level was 119 mg. per 100 c.c., and on May 10, the third hospital day, it was 75 mg. per 100 c.c. From then on a moderate degree of hyperglycemia was almost constantly maintained.

On the fourth day of coma, paralysis of the right upper extremity appeared. The biceps tendon reflex was greater on the left than on the right. The quadriceps femoris tendon reflexes were equal. There was absence of the ankle and abdominal reflexes. Moderate nuchal rigidity and deviation of the head and eyes to the left were present. The Babinski reflex was equivocal on the left and flexor in type on the right. Lumbar puncture again revealed a crystal clear spinal fluid. Initial pressure was 90 mm. of water. The fluid contained 6 lymphocytes per cu. mm.

During the following 10 days no significant change in the patient's condition occurred. Mild hypertension (164/94), rigidity, monoplegia and other evanescent neurologic signs were the outstanding features. Supportive therapy consisted mainly of the parenteral administration of amino acids, carbohydrate, salts and vitamins. In view of the desperate and unrelieved condition and the history of trauma to the head (albeit remote), a bilateral midtemporal trephination of the skull was performed. The dura was found to be normal in appearance on both sides. When the dura was opened the brain herniated into the trephine openings. Its surface was injected but there was no evidence of loculated fluid or blood. Following operation the patient's general condition remained essentially unchanged. On the nineteenth day she became somewhat aware of her surroundings and was able to perform simple movements on repeated command. Slow improvement ensued. She remained lethargic and somnolent but more responsive. Aphasia and incontinence of urine and feces were present. On the twenty-second day a small amount of nourishment was taken by mouth for the first time. Within two weeks she had become ambulatory. However, further improvement was minimal. The gait was shuffling and uncertain, orientation and understanding were limited. Speech consisted only of the difficult repetition of a few words. Swings to moodiness and negativism were frequent. Gradually, continence returned. On December 22, 1950, more than six months after admission, she was transferred, in the same condition, to the home care service of the hospital. At that time she was receiving a mixture of 20 units of regular and 10 units of protamine zinc insulin. Follow-up examination one year after admission disclosed that the patient was leading a totally dependent existence. The gait was shuffling, understanding was adequate, orientation was not complete and aphasia was about 60 per cent. Considerable paresis of the right upper extremity was present, and the Babinski reflex produced slight dorsiflexion bilaterally.

Comment: Permanent cerebral damage is so extensive in this case that the patient's disability is practically total. However, that the patient recovered at all after 19 days of unconsciousness is remarkable. The remote possibility of a subdural hematoma led to cerebral exploration when it appeared that spontaneous improvement was not likely to occur.

Case 3. A 66 year old Negro woman was admitted to the metabolic service at 11:00 a.m. on September 4, 1946, from the diabetic clinic. She had been referred for diagnosis and control at the urgent request of the Social Service Department. The patient was not known to have diabetes mellitus but was a known alcoholic. Diabetes mellitus was suspected because of a moderate amount of glucose in the urine on two occasions.

The patient gave a history of loss of weight, weakness, increasing dimness of vision and polyuria and polydipsia. She was rational and coöperative and appeared to be comfortable. There was evidence of recent loss of weight and dehydration. The pupils were equal but reacted sluggishly to light. Opacities of the lenses were noted, and only gross vision was present at a distance of three feet. The blood pressure was 150 mm. Hg systolic and 90 mm. diastolic. The heart was normal. There was no abnormal reflex and no motor or sensory disturbance. The urine on admission contained sugar (4 plus) and acetone (1 plus). The specific gravity was 1.030. No albumin was present. The level of sugar in the blood was 580 mg. per 100 c.c. At 1:00 p.m. the patient was given 20 units of regular insulin. At 3:30 p.m. the urine gave a 4 plus reaction for sugar, and a trace of acetone. She was given 20 units of regular insulin. From then until 9:00 p.m. the patient received additional regular insulin at intervals until a total of 215 units had been given. At that time she was receiving an intravenous infusion of 5 per cent glucose in saline, and the urine for the first time was found to contain less sugar (3 plus) and no acetone. From then until 3:00 a.m. the urine gave only a 1 plus reaction for sugar, and no further insulin was given. Intravenous infusions of 5 per cent glucose in saline totaling 1,500 c.c. were completed by 12:00 midnight. At 6:00 a.m. on September 5 the patient's condition was noted to be "poor," and "incontinent care" was given by the floor nurse. The urine, obtained via catheter, was free of sugar. Shortly after, the patient was discovered to be in coma. She was perspiring freely and having clonic contractions of the right upper extremity. There were generalized spasticity and rigidity, slow, quiet respirations, grossly irregular cardiac rhythm and conjugate deviation of the eyes to the right. The blood pressure was 180 mm. Hg systolic and 110 mm. diastolic. Fifty cubic centimeters of 50 per cent glucose were administered intravenously without noticeable change in the condition. In 20 to 30 minutes, 100 c.c. of 50 per cent glucose and 0.5 gm. calcium gluconate were given intravenously, again without effect. An attempt at lumbar puncture was unsuccessful, apparently because of the rigidity and the presence of arthritis of the vertebrae. The blood sugar was 136 mg. per 100 c.c. after the intravenous administration of 75 gm. of glucose. The carbon dioxide combining power was 36 vol. per 100 c.c. An intravenous infusion of 5 per cent glucose in saline was instituted, and in three or four hours glycosuria resulted. Coma appeared to decrease, as the patient now moaned and yawned at intervals. Conjugate deviation of the eyes to the right, right lateral rotation of the head and spasticity persisted. Twelve hours after the onset of coma she evidenced a fixed stare, with slow blinking of the eyes and fixed rotation of the head to the right. When the head was turned anteriorly a horizontal nystagmus was noted. The right lower extremity appeared to be more spastic than the left, and the Babinski reflex was positive on the left. An attempt at lumbar puncture was again unsuccessful.

On September 6, more than 24 hours after the onset of coma, the patient's condition remained essentially unchanged. The heart was fibrillating slowly at about 80 per minute. The temperature was 104° F. No focal neurologic sign was present except for slight spasticity of the left upper extremity. The blood sugar was 220 mg. per 100 c.c. Forty-eight hours after the onset of coma the patient became semiconscious. She was mute and resistive, and tended to maintain flexion of the lower extremities and the right upper extremity. There was a positive Babinski reflex

on the left and paralysis of the left upper extremity. Deep reflexes were absent. For the next five days she continued in a semicomatose to conscious state, and exhibited complete aphasia, left-sided hemiplegia and bilaterally positive Babinski reflexes, more marked on the left. During this period the temperature became elevated. Treatment consisted of supportive measures and included penicillin, parenteral administration of amino acids and 5 per cent glucose in saline solution, large doses of vitamin B complex and thiamine chloride, and occasional small doses of regular insulin to prevent acidosis. She was permitted to have moderate and constant hyperglycemia and glycosuria.

On the eighth day after the initial onset of coma, spasticity and left hemiparesis were still present, although they had varied in degree from time to time. Coma again supervened, gradually becoming deeper. This was associated with hyperpnea, which soon changed to Cheyne-Stokes respiration. On September 3, nine days after admission, the patient died.

Autopsy Findings: Autopsy, performed 12 hours after death, disclosed congestion, hypostatic pneumonia and edema of the lungs, especially in the left lower lobe, which contained several small areas of infarction due to embolism. The heart was normal in size and appearance and weighed 275 gm. There was some atherosclerosis of the tricuspid and mitral valves and of the coronary arteries, but no significant narrowing or occlusion of the latter was noted. The aorta contained a moderate amount of atheromatous deposits, especially in the arch. There were congestive changes in the liver and gastrointestinal tract. The spleen was markedly atrophied and weighed only 45 gm. In the pancreas, occasional hydropic degeneration of the islet cells and fibrosis of the islets were observed. The kidneys were grossly normal in size and appearance, but microscopically there was a moderate degree of arteriosclerosis. The left adrenal gland appeared slightly enlarged. On microscopic section the cortices of both adrenals exhibited considerable hyperplasia of the cells of the zona fasciculata and zona reticularis. Areas of fatty degeneration, cloudy swelling, congestion and elastosis of arterioles were also seen in the cortical portions of the adrenal glands.

The changes in the brain appeared to be most significant. The brain weighed 1,120 gm. and appeared grossly normal. The vessels at the base of the brain contained a moderate amount of atheromata and sclerosis. Gross section of the brain disclosed no area of hemorrhage or softening. Microscopic preparations stained with hematoxylin and eosin revealed diffuse changes in practically all portions of the brain. The most extensive alterations were in the nuclei of the neurons, which in many instances were displaced, pyknotic and even fragmented. Other changes noted were perineuronal edema, swelling of axis cylinders, degeneration of myelin sheaths with edema, glial hyperplasia and congestion of blood vessels with vascularization. These lesions were most prominent in the region of the globus pallidus.

Comment: Despite the fact that this patient was elderly and chronically addicted to the use of alcohol, factors which have been said to produce greater susceptibility to irreversible cerebral changes in hyperinsulinism, cellular alteration, not vascular, was the outstanding feature of the microscopic lesions. This increased susceptibility, which has been noted in alcoholism, arteriosclerosis and prolonged chronic infections, need not be due to a direct effect of these conditions on the brain (e.g., vascular degeneration), but may be due to an insufficiency of adrenal cortical (insulin antagonistic) hormones. This would be produced in the elderly by the "adrenopause" of Albright,[12] and in alcoholism and chronic infection by the adrenal

exhaustion of the late stage of Selye's adaptation syndrome.[13] Recent observations of the beneficial effect of adrenocorticotropic and adrenal cortical hormones in the treatment of acute and chronic alcoholism,[14] and the adrenal cortical hyperplasia found at postmortem examination in this case, would tend to corroborate this theory.

Case 4. This was the twelfth admission of a 66 year old male who entered the hospital at 4:00 p.m., October 7, 1950, because of vomiting of two days' duration. The patient was known to have had diabetes mellitus for 11 years. For the past six months he had been taking 15 to 20 units of protamine zinc insulin daily. He gave a history of having been on an alcoholic spree for a week and of having eaten very inadequately during that time. He had taken no insulin for four or five days.

Review of Previous Admissions: First admission, July 21, 1945. Vomiting and abdominal pain; admitted alcoholism; discharge diagnosis, "acute alcoholic gastritis." Urine did not contain sugar. Blood sugar 135 mg. per 100 c.c.

Second admission, April 22, 1946. Vomiting, nervousness, tremors; alcoholism. Urinalysis: sugar, 4 plus; acetone, zero. Diagnosis, "acute gastritis." No insulin therapy required on discharge.

Third admission, July 13, 1946. Vomiting; diabetes "controlled on diet." Admission urinalysis: sugar, zero; acetone, 4 plus. Blood sugar, 63 mg. per 100 c.c. Treated with intravenous glucose in saline.

Fourth admission, December 22, 1946. Weakness and disorientation. Urinalysis: sugar, zero; acetone, 4 plus. Left hospital against advice after two days. Treated with 1,000 c.c. of 5 per cent glucose in saline intravenously.

Fifth admission, March 14, 1948. Acute alcoholism with vomiting and marked tremors; alcoholism and inadequate diet for two years. Urine contained no sugar or acetone.

Sixth admission, July 18, 1948. Alcoholism, inadequate diet, insulin therapy stopped. Urine on admission contained sugar, 1 plus; acetone, 4 plus. Treated with intravenous infusion 5 per cent glucose in saline and 140 units of regular insulin in 14 hours. Gross tremors on admission; blood sugar (July 19), "below 50 mg. per 100 c.c."; blood sugar (July 23), 100 mg. per 100 c.c., with 2 plus reaction for sugar, 3 plus reaction for acetone in urine; 58 mg. per cent July 28, with 3 plus glycosuria.

Glucose Tolerance Test, July 30, 1948

	Blood Sugar Levels	Urine Sugar
Fasting—	85 mg. per 100 c.c.	0
Half hour—	135 mg. per 100 c.c.	0
One hour—	167 mg. per 100 c.c.	2 plus
Two hours—	230 mg. per 100 c.c.	3 plus

Discharged on protamine zinc insulin, units 12 daily.

Seventh admission, November 27, 1948. Weakness, vomiting, abdominal pain. No glycosuria on admission; two days later, 3 plus glycosuria with 120 mg. per cent blood sugar.

Eighth admission, May 7, 1949. Vomiting, tremors, lethargy; no adherence to diet or insulin therapy. Three plus glycosuria, 3 plus acetonuria with *blood sugar 150 mg. per cent on admission.*

5/11/49, 3 plus glycosuria with 170 mg. per cent blood sugar,
5/16/49, 3 plus glycosuria with 120 mg. per cent blood sugar,
5/18/49, 4 plus glycosuria with 53 mg. per cent blood sugar,
5/27/49, 2 plus glycosuria with 93 mg. per cent blood sugar.

Ninth admission, September 11, 1949. Twenty-four hour admission for weakness and vomiting; alcoholism. Three plus glycosuria, 2 plus acetonuria with *blood sugar 80 mg. per cent.* Left hospital against advice.

Tenth admission, November 2, 1949. Nausea and vomiting; no insulin for several days; no glycosuria on admission; blood sugar level "below 50 mg. per cent." November 16: 2 plus glycosuria; blood sugar level, 110 mg. per cent. Discharged on a mixture of 50 units regular insulin and 25 units of protamine zinc insulin.

Eleventh admission, March 22, 1950. Vomiting; on a drinking bout; stopped insulin therapy. Admission urinalysis: 4 plus sugar, 3 plus acetone; CO_2 combining power, 28 vol. per 100 c.c.; *blood sugar 135 mg. per cent.* Given 100 units regular insulin on admission. In five hours a total of 245 units of insulin was given; eight hours later deep coma, which responded to 100 c.c. 50 per cent glucose and 1,000 c.c. 5 per cent glucose in saline intravenously. The following morning, patient again became comatose and had a convulsion, with clonus mainly of the left side. Again responded to intravenous 50 per cent glucose; another episode of hyperinsulinism occurred 36 hours after admission. Again response to intravenous glucose was rapid. Discharged on a mixture of regular insulin, 40 units, protamine zinc insulin, 20 units.

Summary of Previous Admissions: All admissions appear to have been preceded and precipitated by episodes of acute alcoholism. This patient constantly disregarded all rules for the control of diabetes mellitus. There appears to be sufficient laboratory evidence in numerous hospital records and in the clinic record to suspect that a low renal threshold for glucose coexisted with diabetes mellitus in this patient.

Final Admission: Examination disclosed a poorly nourished, elderly male, retching, slightly lethargic, with mild clouding of the sensorium but responsive and cooperative. The conjunctivae and sclerae were suffused and injected. There was a coarse tremor of the tongue and hands. The blood pressure was 140 mm. Hg systolic and 70 mm. diastolic. A soft systolic murmur was heard at the apex; the heart was otherwise normal. Urinalysis on admission revealed 2 plus glycosuria and 4 plus acetonuria. Five per cent glucose in saline solution containing large doses of thiamine chloride was started intravenously, and 30 units of regular insulin were given immediately. Three hours later the urine gave a 3 plus reaction for sugar and 3 plus for acetone, and again 30 units of regular insulin were given. In all, a total of 150 units of regular insulin was given in the first eight hours after admission, until at 12:00 midnight the urine was free of sugar and acetone. During the night an additional 1,000 c.c. (total, 3,000 c.c.) of 5 per cent glucose in saline containing 200 mg. of thiamine chloride were given. Twelve hours after admission, the patient became somewhat confused and restless and had to be restrained. Several hours later deep coma supervened. At this time râles appeared over both lung fields, and the urine contained no sugar, but a 4 plus reaction for acetone was obtained. The blood sugar was 20 mg. per 100 c.c. (no correction for non-glucose reducing substances; true blood sugar level probably zero). Lumbar puncture produced clear spinal fluid under a pressure of 260 mm. of water. No response was obtained with the administration of 50 c.c. of 50 per cent glucose followed by 1,000 c.c. of 10 per cent glucose in distilled water. Later that day, glycosuria again became evident, with slight acetonuria. At 8:00 p.m. the patient had a series of short convulsive seizures. Following this a suggestion of a left-sided hemiparesis was noted. Despite the attainment and maintenance of hyperglycemia, coma persisted without change. After four days of coma, Cheyne-Stokes respiration, nuchal rigidity, slight spasticity of the right upper and lower extremities and complete flaccidity of the left upper and lower extremities were noted. On the fifth day of coma the patient died.

Comment: On at least six occasions where full data are available, this patient entered the hospital with levels of the blood sugar below 150 mg. per 100 c.c. despite a urine content of sugar and acetone ranging up to the maximum of grossly quantitative tests (4 plus). Only prompt discovery of hyperinsulinism on the next-to-the-last admission averted disaster then. The combined presence in this patient of diabetes mellitus and a lowered renal threshold for glucose seems almost unquestionable. This has been a not infrequent occurrence in our experience. If the diabetes is difficult to control (as in this case), the combination is potentially dangerous. The treatment of diabetic acidosis in such patients requires immediate large quantities of glucose and relatively small doses of insulin for obvious reasons. The determination of the blood sugar level within an hour of admission at any hour of the day or night is necessary for the prompt recognition and correct treatment of diabetic complications.

Case 5. A 15 year old Negro girl was admitted to the metabolic service in coma at 11:30 a.m., March 3, 1947. From the age of seven she had had severe, unstable diabetes which required large doses of insulin. In the past six years she had been admitted 13 times to this institution alone. The majority of these episodes were diabetic acidosis, although an occasional episode of hyperinsulinism was seen. At the time of this admission, no history of either the past or the present was available.

Examination disclosed stertorous respirations, unconsciousness with vigorous reaction to stimuli, blood pressure 140 mm. Hg systolic and 90 mm. diastolic, and tachycardia. The remainder of the physical examination was essentially within normal limits. The urine obtained by catheterization contained sugar, 4 plus, and acetone, 3 plus. The patient was given an intravenous infusion of 5 per cent glucose in saline solution and 30 units of regular insulin. At 1:00 p.m. the admission blood sugar was reported to be "less than 50 mg. per 100 c.c."; CO_2 combining power, 64 vol. per 100 c.c. It was realized then that despite the presence of sugar and acetone in the urine the patient was in a state of hyperinsulinism. Partial response to the intravenous administration of hypertonic glucose solution was seen, but shortly thereafter the patient again lapsed into coma, with light convulsions. With continued administration of intravenous glucose the patient gradually became rational enough to offer responses to questioning. However, it was practically impossible to maintain the administration of glucose for more than 20 to 30 minutes at a time. As coma would diminish she would exhibit violent restlessness bordering on maniacal behavior. For the next 18 hours the depth of coma varied with the amount of glucose being instilled intravenously at the time. The blood sugar level could not be elevated above 50 mg. per 100 c.c. During this period about 50 to 70 gm. of glucose were given intravenously.

Twenty-four hours after admission the urine was still free of sugar, the blood sugar was 62 mg. per 100 c.c., and the carbon dioxide combining power was 58 vol. per 100 c.c. The patient was in deep coma and nonresponsive. The respirations were slow, deep and regular; pulse, 112 per minute; blood pressure, 120 mm. Hg systolic and 80 mm. diastolic; rectal temperature, 101.2° F. The pupils were equal and reacted to light. The deep reflexes were equal and hyperactive. There was no apparent motor weakness. Further history was now obtained from the girl's mother. For from two to three weeks the patient had been having frequent mild episodes of hyperinsulinism in the early morning on a dosage of 90 units of globin insulin before breakfast and 60 units of globin insulin before dinner. She had found her daughter unconscious in the morning following an evening of strenuous dancing.

Heroic measures were now instituted to overcome hypoglycemia. A vein was phlebotomized, 50 c.c. of 50 per cent glucose solution were injected, and the arm was restrained manually for over two hours while a solution of 10 per cent glucose was rapidly instilled. After one and a half hours of this therapy the urine gave a 4 plus reaction for sugar. By 3:00 p.m. that afternoon the blood sugar level was 175 mg. per 100 c.c. Despite this attainment of hyperglycemia, the patient's condition improved only slightly. Although she opened her eyes on stimulation, there was no response to questions and no recognition of her familiar surroundings.

On March 5, 48 hours after admission, the mental state remained essentially unchanged. The blood sugar was 290 mg. per 100 c.c., and considerable glycosuria was evident (4 plus). The deep reflexes were still hyperactive and equal. Slight widening of the right palpebral fissure, with slight flattening of the right nasolabial fold and suggestive motor weakness on the right were now present. A positive Babinski reflex was elicited on the left, with an equivocal Babinski response on the right. During that day, restlessness and unconsciousness continued. Toward evening she suddenly became violent, stood up in bed shouting, and was again restrained with difficulty. The following morning, 72 hours after admission, the patient was mentally clear and alert, with no recollection of any events of the preceding three days. At this time the neurologic signs were diminished abdominal reflexes on the right and normal Babinski responses bilaterally. The blood sugar was 395 mg. per 100 c.c., and more adequate insulin therapy was instituted. The remainder of the hospital stay was characterized by the usual difficulty in establishing control of glycosuria and avoiding hypoglycemia. In part, the frequency of the latter was explained by the finding of a lowered renal threshold for glucose. She was discharged finally on a dosage of protamine zinc insulin, 75 units, and globin insulin, 115 units before breakfast daily. Glycosuria was moderately heavy (3 plus) during most of the day. No abnormal neurologic sign was present at the time of discharge from the hospital. An electroencephalogram taken April 15, 1948, one year after discharge, exhibited no abnormality of the brain waves. In the three years since discharge she has been readmitted 12 times. She has never evidenced impairment or deficiency of mentality. However, she does appear to be maladjusted, irresponsible and, in general, something of a behavior problem. This continues to be the major factor, producing a frequent need for hospitalization because of poor diabetic control.

Comment: In this case, despite the length of coma and the focal signs of organic cerebral damage in the post-hypoglycemic phase of hyperinsulin encephalopathy, recovery without apparent residua occurred. As far as present clinical and laboratory examination can determine, complete reversal to normal of the pathologic changes occurred. Whether this and many previous episodes of less severe hyperinsulinism have significantly contributed to the structure of this girl's personality cannot be stated dogmatically. Experience indicates that this is a possibility. The episode reported also illustrates the unreliability of the urine as an initial diagnostic indicator in diabetic persons in coma.

Rapid and reliable means of determining the blood sugar level of all diabetics in coma must be available at any hour if diagnostic confusion is to be avoided.

Discussion

That definite injury to the central nervous system, both temporary and permanent, can be produced by excessive amounts of insulin has been clearly

established and generally accepted. Confirmation of the nature and extent of the lesions has been more than ample.[4, 6, 8, 15, 16, 17, 18] In general, the pathologic changes consist of widespread decrease, alteration and even complete destruction of neurones, especially of the cortex and basal ganglia, proliferation of the glial tissue and petechial hemorrhages. These changes are not actually specific but are sufficiently characteristic to be confirmatory when the history, clinical manifestations and course have indicated hyperinsulinism. The parenchymatous nature of the degenerative changes leads to such pathologic diagnoses as "degenerative encephalopathy" and "toxic encephalopathy." [19] In fact, the lesions are similar to, if not in some cases indistinguishable from, those found in primary degenerative diseases of the central nervous system and to encephalopathies due to exogenous toxins, such as morphine and nitrous oxide.[4, 16]

The mechanism by which insulin produces damage to the brain is poorly understood. Despite the large amount of investigative work on the subject, the explanations are as yet hypothetic. Recent advances in the study of glucose metabolism and insulin physiology, when properly applied, may yield the key to the problem. As previously discussed, the rôle usually attributed to hypoglycemia as sole cause of this condition is disputed because of an occasional lack of parallelism between the level of the blood sugar and the clinical manifestations.[3, 4, 6] To repeat: an insufficiency of glucose in the blood stream may not, under certain circumstances, produce an insufficiency of cerebral cellular content of glucose, and, conversely,[2] a sufficient quantity of glucose in the blood stream does not insure an adequate intracellular content. However, the clinical manifestations and the underlying pathologic changes could be produced by an interference with the transference of glucose from blood to cerebral cell, or with glucose utilization within the cell. In the former instance, the result would be actual cellular glucopenia, and in the latter a failure of glucose oxidation. The phosphorylation of glucose to glucose-hexose-phosphate via its combination with adenosinetriphosphate under the influence of the enzyme hexokinase has been shown to be a prerequisite to the cellular transfer of glucose and its biochemical oxidation.[20] This enzymatic reaction is usually represented graphically as follows:

$$\text{Glucose} + \text{ATP} \xrightarrow{\text{Hexokinase}} \text{Glucose}6\text{PO}_4 + \text{ADP}.$$

An insufficiency of, or interference with, any of the three factors necessary for this reaction to proceed at a proper rate could, if prolonged, produce irreversible cellular damage or death. This effect is entirely limited to the central nervous system because of the dependence of nervous tissue on glucose as a source of metabolic energy. Other tissues can meet all their requirements by the utilization of fatty acids. Recent work has shown that nerve tissue can also oxidize acetoacetic acid and glutamic acid, but apparently not in sufficient quantities to maintain adequate nutrition.[21]

The effect of hypoglycemia, or an inadequate supply of glucose, on the hexokinase reaction appears obvious. As the sole mechanism, it is probably still the most widely accepted cause of the encephalopathy of hyperinsulinism. However, animal experiments with large doses of insulin indicate the possibility of a direct toxic effect of insulin as at least an additional factor.[22] Animals given from 3 to 20 units of insulin per kilogram were maintained in periods of hypoglycemia ranging from six to 15 hours. It was found that the degree and extent of the period of hypoglycemia were not directly related to the outcome. Whether these animals recovered, succumbed or survived with evidence of injury to the central nervous system seemed to be related to the relative quantities of insulin injected. This apparent toxic effect of insulin was not seen even in the presence of large doses when the blood sugar level was maintained at normal levels by the continuous infusion of glucose solution. These experiments suggest that, aside from hypoglycemia, large doses of insulin promote certain reactions in the cerebral cells which lead to serious injury when the blood sugar is low but which are prevented by a normal concentration of blood sugar. Others have commented on the limits of insulin dosage demonstrable in laboratory animals, beyond which death can be delayed by glucose administration but not prevented.[23]

Recent work has demonstrated that insulin accelerates and promotes the hexokinase reaction by abolishing the inhibition of this reaction by anterior pituitary and adrenocortical hormones (inhibits the inhibitors).[24, 25] In this way it aids the initiation of a chain of reactions which leads either to glycogen formation and storage or glucose oxidation. This salutary action of insulin in physiologic amounts on the hexokinase reaction does not preclude the possibility of a disruption of the effect when the quantity of insulin becomes excessive. Investigations along this line might shed some light on the unresolved question of whether the impairment of cellular metabolism is in any part due to a direct toxic effect of insulin. Pending the outcome of such investigations, the use of the insulin-antagonistic pituitary adrenocorticotropic and adrenocortical hormones is suggested in the treatment of hyperinsulinism in which encephalopathy has produced coma unresponsive to glucose administration.

Summary

1. Hyperinsulinism is commonly seen as a result of the injection of overdoses of insulin and rarely as a result of hypersecretion or disease of the pancreas. The use of the term should not be limited to the latter conditions. Its general adoption would eliminate the inaccurate and misleading term, "insulin shock."

2. The terms commonly used in connection with this syndrome refer to various phases and degrees of the encephalopathy always produced by hyperinsulinism.

3. Cases are presented, with appropriate comments, which illustrate the protean manifestations and varied outcome of this condition.

4. The pathogenesis of hyperinsulinism is discussed in the light of newer knowledge of carbohydrate metabolism and insulin physiology.

5. The use of ACTH and adrenocortical hormone is suggested if the encephalopathy does not respond immediately to glucose and there appears to be danger of permanent cerebral damage.

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CIRCULATING EOSINOPHILS IN CARDIOVASCULAR STRESS *

By Myrvin H. Ellestad, M.D., *San Francisco, California,* and Joseph Reed, M.D., *Long Beach, California*

Since the description by Thorn [1] of the eosinophil test for adrenal cortical function and the more general acceptance of Selye's work [2] emphasizing the importance of the adrenal steroids in adaptation to all stress, the level of circulating eosinophils has been studied in many disease states.

Thorn, Roche, Recant [3] and others have shown typical responses to anesthesia, surgical procedures, infections, etc., dependent on an intact hypophyseal-adrenal axis. A few counts following coronary occlusion have been reported.[4] In this study, 44 patients with suspected acute myocardial infarction or congestive failure have been followed with daily eosinophil counts to determine the level of cortical activity.

Mechanism

It has been demonstrated by Selye and others that systemic stress, be it cold, pain, anxiety, infection or starvation, sets up a series of alterations in the body grouped together under the term "general adaptation syndrome." These include tachycardia, fever, sweating, hemoconcentration, elevated sedimentation rate, increased circulating fibrinogen, increased clotting tendency, leukocytosis, lymphopenia and eosinopenia. This chain of events is mediated primarily through the hypothalamus, pituitary and adrenal cortex, but other pathways, still unknown, probably also play an important rôle.

Since the advent of ACTH and cortisone in clinical medicine, the circulating eosinophil count has been accepted as the most accurate index of the changes in output of adrenal steroids. In this study, the increase in circulating cortical hormones is measured by the degree of eosinopenia, which, we believe, gives an approximation of the amount of systemic stress present.

Procedure

Daily counts were done by a modification of the method of Dunger.[5] Oxalated blood was drawn to the 1 cm. mark in the white pipette and diluted with an aqueous eosin and acetone solution. The average of two counts was recorded, all by the same person.

The cases were divided into four groups:

1. Those showing a typical clinical course and electrocardiographic evidence of a through-and-through infarction.

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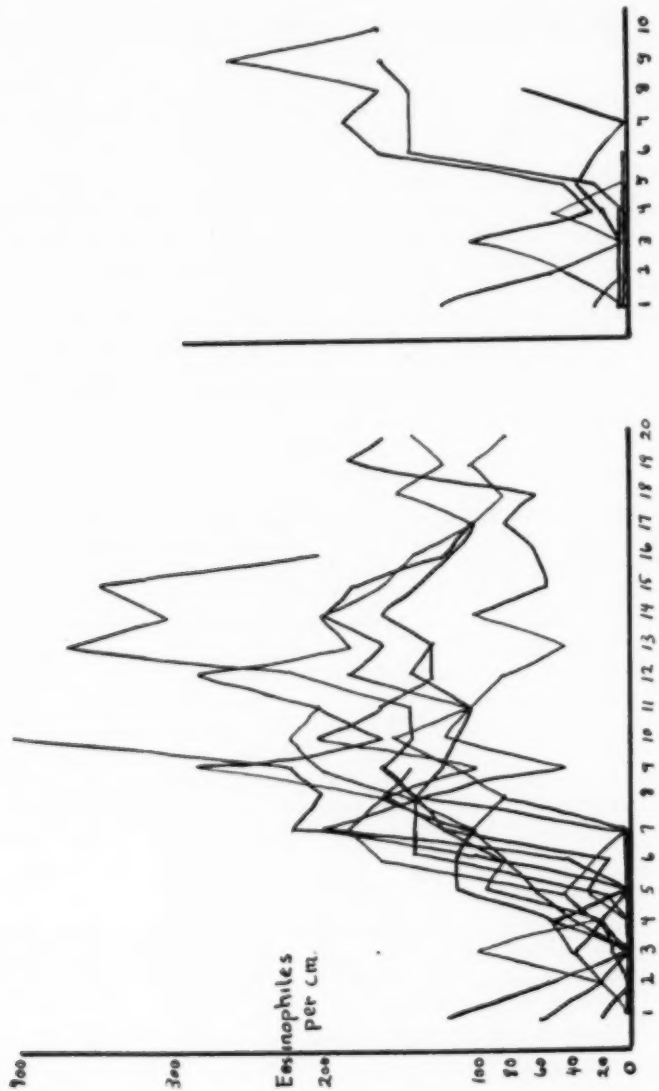

Fig. 1. Through and through infarction.

Fig. 2. Deaths.

2. Those with a typical course and electrocardiographic evidence of subendocardial infarction.
3. Those with acute congestive failure and pulmonary edema.
4. Those with a history suggestive of infarction in which the electrocardiogram was not diagnostic.

To evaluate the degree of eosinopenia, an estimated normal was made from the last few determinations on each patient, as a pre-stress value was obviously unobtainable.

Results

The 17 patients with through-and-through infarctions showed a drop to 20 or below for from two to six days, and an average of five days, and all but one (a fatal case complicated by cirrhosis) were at 20 or below on the second day. About the fifth day came a sharp rise, with a leveling off somewhat below this peak.

Seven of these (figure 1) had definite congestive failure, and from this group came five of the seven deaths. The other two deaths followed a cerebral embolus and a second myocardial infarction. Figure 2 illustrates the course of those who died.

Illustrating this group in figure 3 is a 48 year old welder who, while working, had a crushing, substernal pain, radiating down the left arm and associated with sweating, nausea and breathlessness. Physical examination was essentially negative. The blood pressure was 140 mm. Hg systolic and 80 mm. diastolic; the sedimentation rate 45, and the leukocyte count 14,000. The electrocardiogram showed a recent posterior infarction. The eosinophils dropped to 20 on the second day and stayed low until the sixth day,

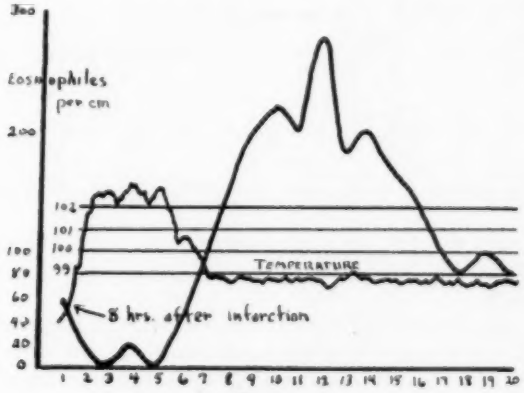

Fig. 3a.

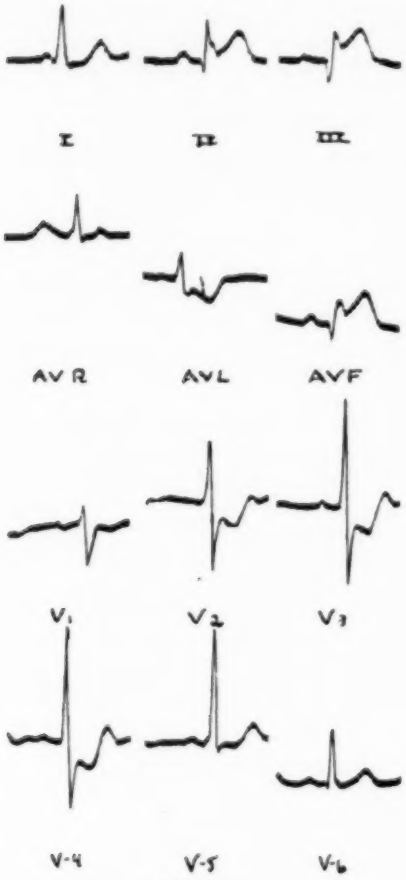

FIG. 3b.

FIG. 3 (*a* and *b*). Forty-eight year old welder with a posterior infarction.

when they started rising to 260, then gradually dropped to about 100. The reciprocal relationship between the eosinophils and fever is typical for this group as a whole.

Thirteen cases with typical histories and electrocardiograms showing "sandwich" T waves and ST segment deviations in the precordial leads were studied. These were diagnosed as subendocardial infarction. The count dropped to 20 or below for an average of one and seven-tenths days and stayed at 50 per cent below estimated normal for an average of three

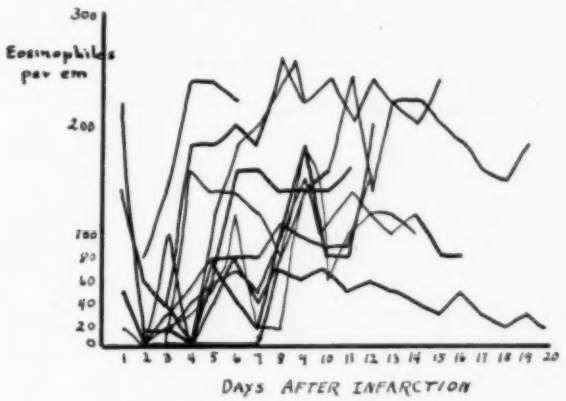

FIG. 4. Subendocardial infarction.

and three-tenths days, two days less than the previous group. The presence of less injured muscle was also reflected by little fever, lower average leukocyte counts and sedimentation rates, and no deaths. Figure 4 shows that the trend was not nearly so consistent as in the first group.

Illustrative of this group is a 68 year old female admitting chest pain on exertion for three years. She awakened with a constricting pain in the epigastrium, chest and left arm, associated with vomiting, sweating and prostration. Nitroglycerin gave no relief. Examination was negative except for tenderness in the right upper quadrant, thought due to distention

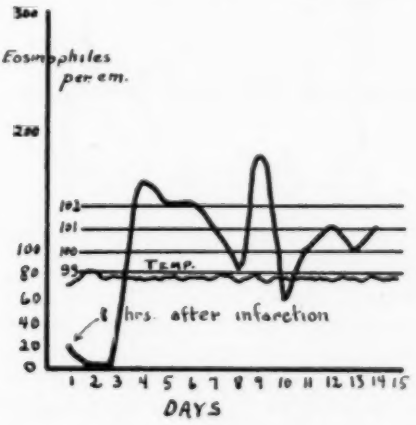

FIG. 5a.

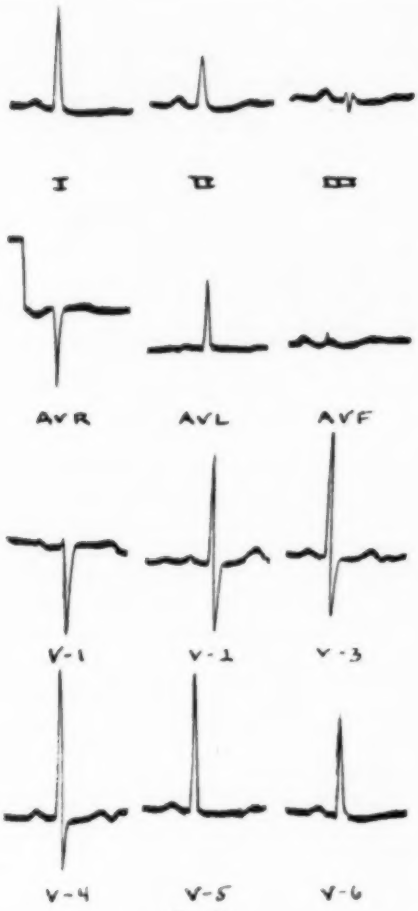

FIG. 5b.

FIG. 5 (*a* and *b*). Sixty-eight year old female with subendocardial infarction.

of the liver. The electrocardiogram suggested a small subendocardial infarction. Figure 5 shows that her eosinopenia lasted three days, then a rise to 160 occurred. She finally leveled off at about 120 and has done well since her discharge.

Four cases of acute congestive failure were studied with initial counts done from four to six hours after onset of the pulmonary edema. Each developed an eosinopenia on the second day but the counts promptly rose to

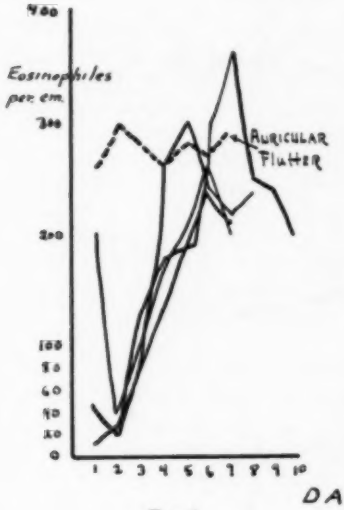

FIG. 6.

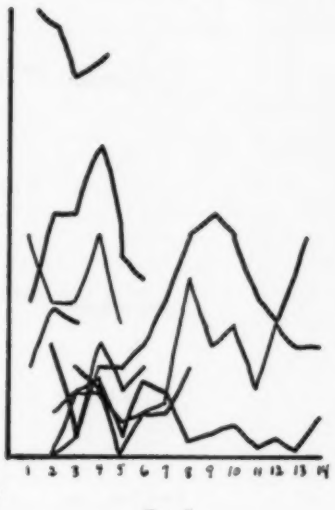

FIG. 7.

FIG. 6. Acute congestive failure.
FIG. 7. Electrocardiogram not diagnostic of infarction.

a high level on the third or fourth. These patients steadily improved and were discharged in a week to 10 days. Listed with these in figure 6 is a case of auricular tachycardia who complained of malaise, weakness and dyspnea but showed no other signs of failure. He showed no significant eosinopenia, as represented by the broken line.

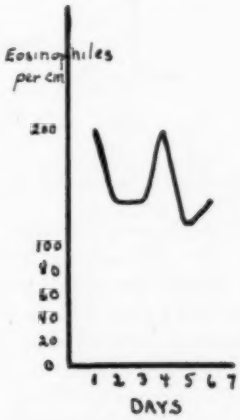

FIG. 8a.

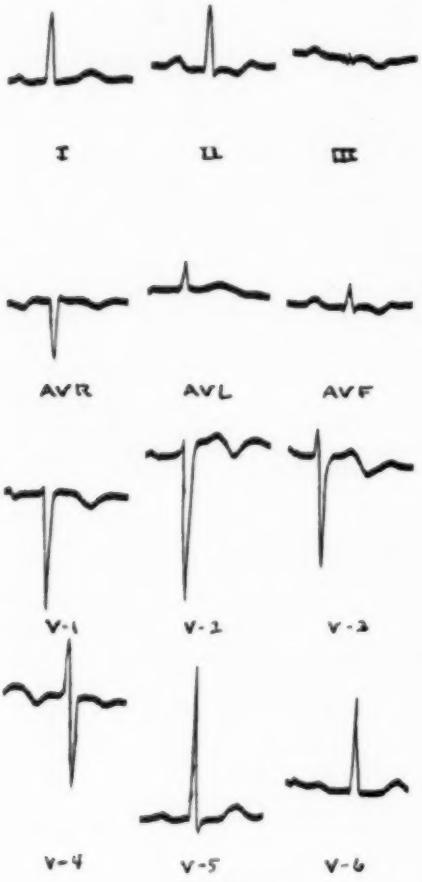

FIG. 8*b*.

FIG. 8 (*a* and *b*). Fifty-eight year old female with angina.

Nine cases with a history suggestive of infarction and presenting inconclusive electrocardiograms were followed for from three to 20 days. The average drop below 50 per cent was only one and three-tenths days, and only five went to 20 or less. Four of these had left bundle branch block, and it was felt that three probably had an infarction, one of whom died in pulmonary edema and uremia on the eighteenth day. In these three, the eosinopenia lasted for an average of three days. (The patient who died showed a drop again to a low level on the eighth day which persisted until

death.) In the others, although cardiac pain was present, a significant eosinopenia did not ensue.

In this group was a 58 year old nurse with systolic hypertension who admitted to angina for eight years. After emotional stress she had sudden dizziness, followed by a squeezing precordial pain radiating into the neck with numbness in the left hand. Examination revealed the blood pressure to be 150 mm. Hg systolic and 90 mm. diastolic, and the pulse to be 90. The sedimentation rate was 34 and the leukocyte count 6,000. Electrocardiogram was suggestive of myocardial damage, but no recent infarction was evident. Because her eosinophils dropped less than 50 per cent, it was concluded there had been no infarction and she was released to work after five days. She is now doing well, and no new symptom or electrocardiographic change has developed.

Also in this group was a 60 year old female who had sudden crushing precordial pain associated with nausea, but no vomiting. Slight sweating and dyspnea were present. There was no previous cardiac history. The blood pressure was 94 mm. Hg systolic and 60 mm. diastolic, and pulse was 88; a few basal râles were heard. The sedimentation rate was 35 and the leukocyte count was 18,000. The electrocardiogram revealed left bundle branch block. It was felt that this patient had an acute infarction because of the leukocytosis and eosinopenia.

Discussion

Roche, Hills and Thorn[6] reported the eosinopenia following major surgery usually was terminated by a marked rise on the third day, which they interpreted as indicating a decrease in cortical activity and a return to normal adrenal cortical reserve. It is interesting that, following myo-

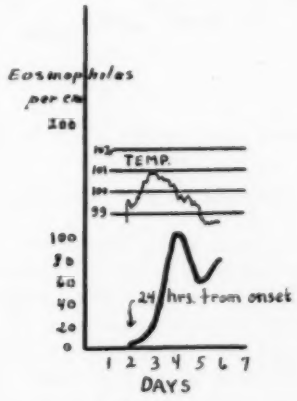

Fig. 9a.

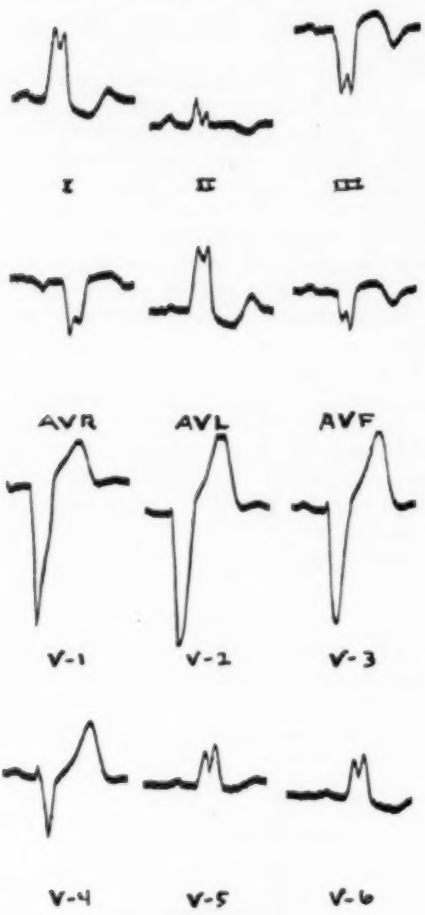

FIG. 9b.

FIG. 9 (*a* and *b*). Sixty year old female with left bundle branch block.

cardial damage, this rise occasionally did not occur until the seventh or eighth day, with the average on the fifth. It appeared that the number of days of eosinopenia roughly paralleled clinical signs of difficulty, such as congestive failure, fever and continued pain.

In many cases of suspected infarction, the history of pain, a symptom often hard to evaluate, is the main key to diagnosis and prognosis. As the pain alone did not produce much depression of eosinophils, it might be that

the amount of actual stress could be estimated by the eosinophil curve as well as by the old criteria, the leukocytosis, elevated sedimentation rate and fever. In the presence of equivocal electrocardiographic findings, it may be of value as an adjunct in diagnosis. We hope that after further study it may also aid in determining the extent of muscle destruction.

It is well to reëmphasize that the drop in eosinophils is a nonspecific phenomenon and will in no way aid in differential diagnosis when infectious processes and other types of stress are concerned.

Summary

The eosinopenia following cardiovascular stress was determined and its possible value as an adjunct to diagnosis and prognosis was discussed.

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SALT DEPLETION SYNDROME WITH INCREASING EDEMA OCCURRING DURING MERCURIAL DIURETIC THERAPY*

By James S. McLester, M.D., F.A.C.P., and Howard L. Holley, M.D., F.A.C.P., *Birmingham, Alabama*

Electrolyte imbalance is sometimes produced by the administration of mercurial diuretics. This is an expression in large part of the depletion of the salt content of the body's extracellular fluid, and there may result a salt depletion syndrome similar to that described by Schroeder.[1] This is usually seen in patients who are handicapped by a preëxisting diminution of renal reserve and is manifested clinically by lassitude, apathy, anorexia, nausea and failure of renal function.

In addition to these phenomena, an increasing edema was seen in three of our patients to whom large amounts of mercurial diuretics were being administered. We believe this is the first reported incidence of this unusual syndrome. The purpose of this paper is to tell of these observations.

Case Reports

The first patient was a 55 year old white male who suffered myocardial infarction one year before admission and subsequently developed cardiac failure. During this interval he had subsisted on a "salt free" diet providing less than 1 gm. of sodium chloride daily and had been given two to three intramuscular injections of Mercuhydrin weekly. This was in addition to apparently adequate digitalis therapy. During the three months before admission it had been thought advisable to increase the Mercuhydrin to daily injections. Approximately three weeks before admission it was observed that he was gradually gaining weight, and edema appeared in the legs and presacral area. There had been progressive oliguria during this period. He became disoriented and increasingly somnolent.

It was quite evident on admission that the patient suffered from progressive renal failure with uremia. The urinary output was 300 c.c. during the first 12 hours after admission. The non-protein nitrogen was 160 mg. per cent, the serum sodium was 120 mEq. and the serum chloride was 67 mEq. Evidence of acidosis was present. A tentative diagnosis of salt depletion syndrome was made, and 1,000 c.c. of a 5 per cent sodium chloride solution given. Diuresis followed, and all evidences of uremia disappeared.

The second patient was a 64 year old colored male with congestive heart failure secondary to hypertensive cardiovascular disease who had been followed in the outpatient clinic. There had been adequate digitalis therapy with "salt free" diet and the occasional intramuscular administration of mercurial diuretics. This therapy had been continued with only minor alterations for approximately one year. One month prior to admission to the hospital it had been found that, to maintain an adequate dry weight, he required Mercuhydrin, 2 c.c. twice weekly, but even this was soon of no avail. His edema increased and he was admitted to the hospital with a

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history of disorientation and rapidly increasing edema. There was oliguria with generalized edema extending to the upper extremities and the face. He was comatose and there was a uriniferous odor to the breath. The non-protein nitrogen was 188 mg. per cent; the creatine, 5.5 mg. per cent. The serum sodium was 121 mEq., potassium 6.5 mEq., chlorides 70 mEq. and carbon dioxide combining power was 12 mEq. Uremic coma was obvious.

It was thought that this patient's uremia was due to a low salt syndrome, and an adequate restitution of electrolyte content of extracellular fluid was attempted. Five hundred cubic centimeters of 5 per cent solution of sodium chloride were administered intravenously, and during the next five hours there was an increase in the urinary output. Diuresis followed, but the patient was found dead in bed several hours later. At autopsy the findings were those of congestive heart failure apparently secondary to hypertensive cardiovascular disease. No adequate cause was found for the sudden death. We believe that this represented a low salt syndrome with hypervolemia which resulted in myocardial failure before adequate therapy could be attained.

The third patient was a 43 year old colored male who had been in the hospital 13 months previously with congestive heart failure. At that time he was in congestive failure secondary to hypertensive cardiovascular disease, with possible chronic healed pyelonephritis. This latter diagnosis was based upon the history of urinary calculus with repeated bouts of urinary infection. He had been maintained on adequate digitalis therapy with a low salt diet and was later given injections of mercurial diuretics, 2 c.c. once each week. He had apparently been properly stabilized over a period of one year. The patient was thoroughly coöperative and observed closely the dietary regimen, which provided an intake of approximately 500 mg. of sodium daily. During his weekly visits to the clinic he showed no evidence of failure. He discontinued his visits to the clinic about one month prior to the second admission to the hospital and was treated at home by his local physician.

He was admitted to the hospital with generalized edema. During the previous 10 days he had been irrational and somnolent. He had been treated by his local physician during the two weeks prior to admission with Mercuhydrin injections twice daily, 2 c.c. each, digitalis and a "salt free" diet. There was marked oliguria, the edema became more marked, and evidences of uremia appeared. On admission to the hospital the patient was irrational, and there was a uriniferous odor to the breath. The non-protein nitrogen was 140, the creatine 6 mg. per cent. The serum sodium was 120 mEq., potassium 5.5 mEq., and chlorides 69 mEq. per liter. The carbon dioxide combining power was 10 mEq. There was only a small amount of urine in the bladder, and this was highly colored. The patient was given 500 c.c. of 5 per cent sodium chloride solution, and diuresis followed. The edema subsided, and the symptoms of uremia rapidly disappeared.

Discussion

The development of uremia after the prolonged administration of diuretics has been reported previously.[2] A true salt depletion syndrome is produced which is similar to that observed after sodium depletion therapy in hypertension. Renal insufficiency is apparently the underlying cause.

The primary cause of this syndrome seems to be the depletion of sodium chloride from the extracellular space.[1] This deficiency can be produced by dietary deprivation or by the excessive loss of this salt after diuretic therapy. Sodium chloride is the principal electrolytic component of the extracellular fluid, and any change in its concentration will presumably disturb the established equilibrium between this space and that of the larger intracellular

fluid compartments.[3] When there is depletion of this salt the extracellular fluid becomes relatively hypotonic.

As this change takes place, it should follow that the extracellular fluid volume becomes difficult to maintain, the fluid being attracted into the intracellular fluid space by its relatively high electrolyte concentrations. Thus, the extracellular fluid volume falls and the peripheral blood becomes concentrated and increasingly viscous. As a direct result of these changes, the effective renal glomerular flow diminishes and nitrogen retention ensues. Obviously this is more likely to occur in a patient with preëxisting renal impairment.

As the syndrome progresses, fluid enters the intracellular space, with resulting engorgement of this space. This explains partly the increase in weight which occurs after salt depletion. Dock has offered an explanation of this paradoxic phenomenon of increasing edema after salt depletion by assuming that the mechanism which initiates maximal reabsorption of sodium by the renal tube also evokes maximal water reabsorption, and that this occurs even after sodium depletion has robbed the body of considerable electrolyte.[4] Sodium excretion normally equals sodium ingestion, with a lag of some days in the establishment of equilibrium when the intake is raised or lowered. Sodium excretion in sweat and urine falls markedly when sodium intake is restricted or sweating has been profuse. If serum sodium is reduced by diet at a time when the mechanism for fluid retention is being powerfully stimulated by severe heart failure, edema increases or remains stationary and uremia develops. Salt administration then may be essential to prevent death. Fortunately this does not occur very often.

Under the conditions described, often attributed to "intractable heart failure," the administration of hypertonic salt solution may be lifesaving. Large amounts must be given to replace the seriously depleted extracellular fluids. At times, 50 to 75 gm. of sodium chloride have been given before improvement became apparent. The onset of diuresis soon after administration of the salt heralds the establishment of normal fluid equilibrium.

Summary and Conclusions

A salt depletion syndrome accompanied by increasing edema and evidences of uremia has been described and the probable cause of certain paradoxic phenomena is discussed. Evidence is presented to show that the administration of sodium chloride in such cases may be a lifesaving measure.

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THE MEETING-PLACE FOR INDUSTRIAL HEALTH *

By DWIGHT O'HARA, F.A.C.P., *Boston, Massachusetts*

MANY of you are familiar with a series of articles now being printed in the *New England Journal of Medicine* under the heading, "Fifty Years of Medical Progress." A subheading appears with each article which places its treatment in one of two categories: medicine as a *science*, or medicine as a *social instrument*. This differentiation provides a helpful approach for many of the subjects with which we concern ourselves. Within such a classification, industrial health may be considered as a social instrument as well as a science, and it is with this viewpoint that I undertake its present consideration.

Social instruments are created by the need and the thinking of society. The product of the thinking is like the product of an assembly line: it varies from year to year in its attempt to create new and presumably better standards or styles. The standard or style at any given time may mark the thinking of that time as clearly as the Model T Ford marked the transportation of the early twenties, or the derby hat marked the well-dressed man of an earlier decade. We tend to be amused by the styles of by-gone days, yet each period may have things which were done superlatively well. A century ago physicians were uncritical and bacteriologically unclean, but they excelled in clinical observation and in the descriptive use of the English language. One might expect those who had practiced among cotton workers to have observed and described the disease now called byssinosis, and so they did. In 1846 Dr. John O. Green of Lowell delivered an address before the Massachusetts Medical Society entitled "The Factory System in Its Hygienic Relations," [1] from which the following paragraph is of interest:

> "The French physicians describe one class of their work people worse situated in a sanatory point of view than the rest, the batters of cotton in the fine mills, whose occupation obliges them to inhale much dust and flue. Whether it be the dust contained in the raw cotton, apart from the cotton flue, or this latter itself, which ruins the health of those engaged in the process, the decay of their health is ever certain and an established fact. They complain of dryness in the mouth and throat, and are seized sooner or later, with a cough gradually increasing in severity. The cough is the first symptom of a slow and formidable disease of the chest, which is always relieved on abandoning the work, and altogether cured at its commencement, if the employment be not resumed. The disease, in the progress of its development, assumes all the characteristics of Phthisis, and the medical men in the manufacturing districts call it Cotton Phthisis, and some Cotton Pneumonia."

Here are described the dry cough, and the tendency of this type of pneumoconiosis to disappear with cessation and reappear with resumption of exposure, characteristics that are commented upon in modern textbooks.[2]

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 13, 1951.

Dr. Green clearly recognized the industrial origin of his "Cotton Phthisis"—he knew it was bad—he deplored the long hours of labor which then prevailed, as well as the employment of children, but it never occurred to him that the "Factory System" could be altered in an engineering sense. That was not the critical need of his day, yet Dr. Green's cotton phthisis was so completely eliminated in the last half of the last century that the disease had to be rediscovered (and of course renamed) in the present. This may have been incidental to general improvement in living and working conditions, or it may have been an improvement forced by the desire of employers to tap the best available labor. Whatever the explanation, it reminds us that disease may be recognized in proportion to several circumstances: its actual prevalence, or the intensity with which we seek to find it, or the social discomfort and unhappiness which it produces. This last especially applies to industrial diseases of today.

Our industrial evolution has now become so complex that it is no longer possible to identify the origin of our thinking, but, whatever its origin, our thinking has been recently marked by an increased willingness and desire to foster industrial health. As evidence of this increased willingness and desire, it has now been provided that workmen be compensated for industrial injury and industrial illness, and in some of our states also for non-industrial sickness disability, all as a matter of social expediency and quite apart from any private economy of the individual. In addition to these statutory arrangements, we cannot fail to be impressed by the hundreds of health and welfare plans now in operation, and increasingly written into the contracts between labor unions and employers; they emphasize the importance now attached to industrial health by millions of Americans.

The effectiveness with which some of these modern provisions can be administered depends primarily upon the philosophy of the medical service that is brought to bear upon them. To a surprising degree, we doctors have become responsible for the quality of social activities which have not been of our making but which have been initiated by the need and the thinking of our time. Rightly or wrongly, and whether we like it or not, this is so, for society can turn to none but the doctor for the validation of sickness. This same social thinking has also involved industry, for in the years ahead it must increasingly pay the cost of illness among its workers. Industry knows this and is therefore beginning to ask the medical profession whether it can prevent illness, just as it has already been asking the engineering professions whether they could prevent toxic and mechanical exposures to sickness and injury. The coming of non-industrial sickness disability laws now sharpens the point of this question and lays it squarely on our doorstep. Let us assume that industry has asked us: Can we prevent illness?

What sort of answer can we make? We can prevent smallpox and diphtheria, yes, but smallpox and diphtheria do not ordinarily inhibit industrial production, so this kind of good-health news is not pertinent to the

thinking of the day. It is of historic importance, but it is already taken for granted by society. Can we prevent, control or ameliorate the commonest cause of absenteeism—respiratory infection? A direct answer to this question must still be evasive and equivocal, but it need not be completely negative. What we are really being asked is whether we can prevent those things that now add unnecessarily to the cost of industrial production. Respiratory infection is an almost universal human experience. Although it may be pathologically trivial, it aggregates impressive totals of lost time, and these totals in turn are influenced by age, job or general physical condition. Aging alone can account for cardiorespiratory episodes that may be controlled by job placement. Alcoholism is a social problem primarily because it sharply interferes with the industrial or occupational potential of its victims. When the question has been expanded to include all these things, we may reply that it has been amply demonstrated that we can reduce the cost of production under a great variety of circumstances, by being ready and willing to establish and supervise industrial and mercantile medical and health services. It matters little whether such services are financed or sponsored by employers, by employees, by physicians, by private or by public groups—there are successful examples of all types of sponsorship. The thing that matters is whether they are honestly and efficiently operated, and whether enough doctors are ready and willing to undertake this sort of service as part of their routine activity.

Those who have tried it believe that even part-time services in small plants can be made to reduce the cost of production with a good deal of certainty. O'Connor has discussed this [3] and has stated four essential requirements for success in small plants, as follows: "(1) The medical personnel must be truly interested in developing a real industrial health program; (2) the medical service must come into the plant; (3) the program must have management interest and support, and (4) the primary aim must be the good of the employees." All doctors will accept points 1, 3 and 4 of this tetralogy; they are worth mentioning to a medical audience only because they are excellent tags with which to identify what may be the matter with health services in small plants that have gone wrong. Point number 2, on the other hand, may meet with some resistance from doctors who have allowed themselves to reach the stage of expecting all patients to come to their offices, hospitals or clinics. This second point, that "the medical service must come into the plant," however, is pretty well agreed upon by all who have had first-hand experience with it. From the point of view of records alone, no hospital, clinic or doctor's office can hope to tabulate the information always available at the place of employment: information on new and changing processes, on production volume, or on the psychologic or toxic hazards of a particular job. Knowledge of these things is basic to any medical control of cost, and knowledge of these can be had only at the plant. Furthermore, it commends itself as a general

principle in the practice of medicine for the doctor to be familiar with the patient's environment.

Unless we, as doctors, have confidence that we can reduce the cost of production, we are not in a strong position to promote industrial health. With such confidence, however, we have an unlimited field into which medicine may be expanded. Perhaps our greatest embarrassment is that, as individuals, we are preoccupied with our present activities; we are not seeking expansion, but here at our front door unquestionably is a great vacuum. The question of shortages of doctors has been agitated a good deal lately. The present shortage in medical manpower is due not to curtailment in the numbers of medical students, as has been said in ignorance, but to the fact that there are now a great many more things that doctors are called upon to do. Service in industry is only one of them; government services, insurance companies, private and public funds and foundations, universities and others who have little or nothing to do with sick people are all anxious to adapt medicine to their own particular purposes. This is all because medicine has become a social instrument and can be effectively used as such.

When we turn to industrial health as a science, we find ourselves in a field that challenges more directly the interest and skill of all practitioners of medicine. As Dr. Strong pointed out to this assembly in Boston a year ago,[4] industry is "vitally interested in the increasing incidence of coronary disease and in the tendency to award compensation to a greater percentage of these cases." Gastroenterologists, psychiatrists and others may be likewise involved in the application of our knowledge of cause and effect to occupational environment. Much of today's medical care revolves about things which, although they may be non-industrial in origin, can nevertheless become industrial liabilities, and our scientific knowledge of etiology may then become decisive.

Not only in the heavy and large industries, but in the small plants as well, there lurk many of those rewards that bring joy to the heart of the diagnostically inclined physician. Lead poisoning, that syphilis of industrial medicine, is always possible in the wake of the ever widening use of this now precious metal. Such new and exciting diseases as those following exposure to beryllium have been recognized as hazards in small plants as well as large. A medical awareness of the fact that dusts and other atmospheric pollution, both in and out of doors, may aggravate conditions to which large numbers of people are predisposed, could go a long way toward civic and industrial control of those unpleasant and probably harmful contaminants with which most large cities are now plagued. There are a great many interesting and desirable results to be expected, when and as medical interests and services appear in our industrial life. At first they may appear as by-products, but in American business by-products frequently become main products, and so it could be with services like these.

No reference to industrial health as a science would be complete without mention of the splendid facilities for medical research which are now established and in operation. Research is not something that simply flows when you turn on the faucet, but when fortunately timed and directed it is one of our great tools, and none is more aware of this than industry. It was industrial support that led to the great contributions of the late Leroy U. Gardner at the Saranac Laboratory of the Trudeau Foundation. Industry established the Kettering Laboratories in Cincinnati, and the United Mine Workers established by a five-year grant the Cardio-Respiratory Laboratory at the Jefferson Medical College Hospital in Philadelphia. These represent research at its best, focused upon definitive problems and capable of expansion as the ramifications of the problem expand.

Now I come at last to an explanation of the title of this paper. To be completely honest, the title was phrased before the paper was written. It does not seem to me that industrial health is going to be best served by the promotion of industrial medicine as another specialty, with boards, certificates and residency programs. That is not the road to usefulness. Such promotion would tend to isolate still further the discussion and the practice of the subject, whereas the numbers who participate are already too limited. The "qualified" group would become exclusive, when the urgent need is to make it inclusive. In an industrial nation, the field is too large to be covered by anything less than the entire medical profession, and the entire medical profession should be encouraged to interest itself. The meeting-place for industrial health is more than a forum for toxicologists, more than a medical meeting where occupational diseases are discussed; it is an assembly line at which one group after another may add its own particular and specialized touch to the final product. Not all of these groups are medical; there are insurance carriers, for example, who have been far ahead of us in the emphasis placed on rehabilitation, and who in some instances have also held advanced preventive concepts. We think of preventive medicine as something with which we can prevent or reduce pathology, morbidity or mortality. The modern industrial point of view is more inclusive—it is the prevention of *loss*. Because industry is beginning to appreciate that pathology, morbidity and mortality contribute to economic loss, we who are interested in preventive medicine have powerful allies among those who seek the primary ways and means of preventing loss. There are several varieties of engineers on this assembly line; if we do not encounter them at some of our meetings, we are missing part of the crowd. There are those who do not necessarily have a technical background of their own, but who acquire highly useful knowledge and proficiency in the borderlands between medicine, physics, chemistry and industry. They call themselves industrial hygienists, and they are experienced and effective workers in the field of industrial health. There are enlightened representatives of both management and labor (as well as many still unen-

lightened) whose accomplishments and potential accomplishments may well surpass all others. There are those who administer the workmen's compensation laws in our various states and in their various forms, whose undoubted social and economic wisdom may come to naught if it be unsupported by the intelligent application of medical information. The meeting-place for industrial health is here in this assembly, it is everywhere that doctors meet, it is wherever medical care available to the working man and working woman is discussed, for medical care is the essence of health. American medicine needs industry, because this is an industrial nation and because industry is becoming the focal point for the medical care of the majority of American workers.[5]

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GOLD THERAPY FOR RHEUMATOID ARTHRITIS: A CURRENT EVALUATION *

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In recent years, the value of gold salts in the treatment of rheumatoid arthritis has been recognized by most investigators who have studied the problem impartially. These compounds continue to be a useful tool in spite of the dramatic antirheumatic effects of pituitary adrenocorticotropic hormone (ACTH) and cortisone. The employment of these hormones has not extended far beyond the experimental stage. There are potentially dangerous side effects and remissions are short lived; probably not more than 25 per cent of those treated obtain prolonged benefit, according to Hench.[1] Great pressure is being exerted upon the medical practitioners throughout the country by sufferers from arthritis for a trial with these "new drugs." The relative infrequency with which any enduring improvement is noted warrants caution on the part of the physician who plans to administer them. Hench and others have done much to stimulate thinking about rheumatoid arthritis, and it is hoped that in the not too distant future the etiology of the disease may be apparent and its cure or prevention possible. It may be that some of the plans now being studied for joint or alternate use of ACTH and cortisone, with a tapering off period, will solve many of these problems.

These observations seem to make an evaluation of gold therapy for rheumatoid arthritis especially appropriate at this time. In this paper there will be a brief summary describing the development of this form of treatment, followed by a discussion of hypotheses regarding its mode of action, indications and contraindications, results to be expected, management of the individual patient, and toxic reactions and their treatment.

The fact that unduly large doses of gold compounds were used initially in the treatment of pulmonary tuberculosis and later of rheumatoid arthritis is unfortunate, because the excessive size of these doses was responsible for most of the more severe toxic reactions which alarmed a large part of the medical profession. This fear has prevented many from using a form of treatment which is helpful to a large percentage of patients with rheumatoid arthritis. In 1924 Mollgaard [2] of Copenhagen was administering 1,000 mg. of gold sodium thiosulfate (Sanocrysin) per week for pulmonary tuberculosis. This is equal to the quantity now given during four or five months in the treatment of rheumatoid arthritis. Slightly smaller doses of Sanocrysin were reported by Secher [3] in a series of cases of rheumatoid arthritis and by Faber [4] in the treatment of pulmonary tuberculosis.

The first careful studies dealing with gold salts for rheumatoid arthritis were begun in 1928 by Jacques Forestier of France, using sodium aurothio-

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propanol sulfonate (allochrysine). He reasoned that gold probably served to stimulate the defense mechanism of the body in tuberculosis and might behave similarly in rheumatoid arthritis. This idea was given further support by the work of Feldt [5] in Germany. Feldt showed gold to be effective in relieving rabbit infections if it was injected some time after inoculating the animals with bacteria, but to be without benefit if given at the time of the inoculation.

After several preliminary papers, Forestier [6] in 1934 recommended sodium aurothiomalate (Myochrysine) and aurothioglucose (Solganal-B) as the most useful agents in the treatment of rheumatoid arthritis. He recommended initial small doses and then 100 to 200 mg. weekly, until 1.5 to 2 gm. were given. Repeated series with intervals of two months without chrysotherapy were advised. In 1935, Forestier [7] reported a series of 500 cases treated with gold salts with four cases of intoxication. Two patients had agranulocytosis and two thrombocytopenic purpura, one of whom died. Forestier believed 70 to 80 per cent of his patients responded favorably and indicated that a greater degree of improvement occurred in the early cases than in those of more than two years' duration. By 1935, this investigator recommended a maximal weekly dose of 100 mg. and emphasized the importance of small initial test doses.

Pemberton [8] in 1935 favored doses of 250 to 500 mg. of gold salts per week, the maximum for one course being 3,000 mg. It is not surprising that toxic reactions were frequent, considering the large weekly injections.

Hartfall [9] and collaborators, in 1936, claimed striking improvement or cure in 80 per cent of their 750 cases and urged a maximum of 100 mg. of a gold compound per week. This became the accepted standard.

In 1942, Freyberg [10] and co-workers, after exhaustive studies of the metabolism and excretion of gold, concluded that large amounts of this substance were retained in the body during the period of its administration. They observed that, when a weekly dose of only 50 mg. was used, urinary excretion of gold continued for only four or five months instead of one year, as occurred with 100 mg. weekly, even though the totals were equal. Following this work, the trend in this country has been to recommend the 50 mg. weekly dose. Some workers have suggested that 25 mg. per week may be adequate. More recently, after a total of 1 gm. has been given by weekly injections of 50 mg. each, a maintenance dose of 50 mg. every three or four weeks has been suggested. This has become the practice of the author, as results seem to recommend it as sound.

After nearly 25 years of gold therapy for rheumatoid arthritis, there is no conclusive evidence regarding the manner in which these compounds produce beneficial effects, so that their employment remains on an empiric basis. Studies by Bertrand [11] and associates, in 1948, using a radioactive isotope of gold, showed some selective uptake by the synovia and articular tissues, similar to that observed with stable gold, although this uptake was

not nearly so great as by the kidney, liver and spleen. When a chemical arthritis was produced in rabbits, there was a greater concentration of gold in the synovial membranes than in the corresponding tissues of normal rabbits. Biopsy following the administration of gold also demonstrated a selectivity for the synovia of active rheumatoid arthritis. Kersley [12] suggested that gold produces its effects because of its affinity for the reticuloendothelial system, thereby altering the immune body response. It is highly unlikely that the effect of gold results from any direct antibacterial action. Block [13] et al. endeavored to relate the concentration of gold in tissues of the rat to the respiration of that tissue as measured by oxygen consumption. It was found that the inorganic compounds, gold chloride and gold sodium thiosulfate, did inhibit in vitro oxygen utilization in rat liver and kidney slices, whereas the organic compounds, sodium succino-aurate, gold sodium thiomalate and gold thioglucose did not produce this effect.

Freyberg [10] and associates, in 1942, reported thorough studies of the metabolism of gold when injected into human beings, using various compounds. They found that, during therapy, 75 per cent of injected gold is retained in the body, whereas 25 per cent is excreted, largely in the urine, small amounts in the feces. It was shown that the amount of gold in the blood plasma (almost exclusively in the protein fraction) was determined by the individual dose, whereas the total amount retained, that is, the amount in the tissues, increased with prolonged administration. Excretion of gold continues for many months after cessation of injection; 12 months after the 100 mg. weekly dose, only five or six months after the 50 mg. weekly dose. This fact would indicate that the smaller dosage, if effective, is to be preferred, as it would shorten the duration of toxic effects, demonstrated to correspond to the persistence of gold in the tissues. The above group found that patch tests for hypersensitivity were of no value as an indicator of tolerance or lack of it for gold salts. They concluded that the most useful compounds were those well absorbed from the site of injection and capable of remaining in the circulation sufficiently long to be transported in effective concentration to the site of action. It was their belief that gold sodium thiomalate and gold sodium thiosulfate best fulfilled these requirements. Freyberg and collaborators stated that the only therapeutic value of gold in rheumatoid arthritis was that of reducing or arresting joint inflammation. Relapse was observed to occur frequently when excretion of gold no longer occurred, indicating that tissue content was zero or only a trace.

As rheumatoid arthritis is usually a chronic progressive disabling disease, every means of treatment which can demonstrate a favorable response must be considered, weighing the possible benefits against any risks entailed. It should be understood that gold therapy does not represent a panacea, but simply a useful instrument when controlled by careful clinical and laboratory supervision. It does not, of course, obviate the necessity of instituting all

the usual measures for improving the patient's general condition and resistance. These include psychotherapy, rest, high vitamin well balanced diet, orthopedic measures, physiotherapy, iron or blood transfusion when indicated, and salicylates for pain. Best results are obtained when therapy is instituted early in the disease, as observed originally by Forestier [7] and more recently emphasized by Adams et al.[14]

Gold salts are beneficial in the treatment of rheumatoid arthritis and its modifications, Still's disease, Felty's syndrome and so-called "infectional arthritis," a clinical variant of rheumatoid arthritis. It is difficult to evaluate the response of this last condition because of its natural tendency to recovery after a few weeks, but the author has observed a distinctly favorable alteration in such cases when gold has been instituted after progress had reached a standstill with conservative measures. Forestier [7] reported improvement when gold was administered to patients having rheumatoid spondylitis. However, the consensus in this country contradicts this view and indicates that better results are achieved with roentgen irradiation. Ragan [15] et al. state that rheumatoid arthritis with psoriasis responds less favorably than rheumatoid arthritis alone. The author has observed an excellent result in one patient who had a gradual or subacute onset of pain, swelling, tenderness, and nodular formations over the fibrous tissue of muscles, tendons and joints, most pronounced in the forearms and legs, but not sparing other areas. Essentially no joint involvement was present.

Whereas the chance of marked improvement or "cure" is greatly enhanced if gold is used early in the course of rheumatoid arthritis, when joint swelling has just begun, much relief can be expected in the later stages, especially if some degree of inflammation remains. Patients in whom the disease is of long duration but quiescent will not be improved. Whereas the presence of an increased sedimentation rate of red blood corpuscles has been used as significant of arthritic activity, this test actually constitutes a better yardstick of the response to treatment.

Contraindications to gold therapy consist of severe diabetes mellitus, nephritis—especially with evidence of activity or azotemia, ulcerative colitis, pregnancy, specific allergy, significant hepatic disease, a history of exfoliative dermatitis, blood dyscrasias and a hemorrhagic tendency.

When planning the treatment of a patient with gold salts, the above indications and contraindications should be remembered. In addition, for future reference, one should evaluate the patient's condition with respect to pain, joint swelling, joint deformity, functional activity, anemia and probably body weight. Observation of changes in the manifestations during treatment assists in establishing a sound record of results.

If the above criteria bearing upon the use of gold have been satisfied, treatment may be initiated. Myochrysine and Solganal-B, used intramuscularly, appear at present to be the preparations best suited for rapid absorption and transmission to the site of therapeutic effect in good concentration.

The author's experience has been limited to the use of Myochrysine. The first injection consists of 10 mg. administered deeply intramuscularly into the buttock. Unless there is some evidence of drug idiosyncrasy, a 25 mg. dose is given one week later, followed by 50 mg. after an equal period of time. The 50 mg. dose is repeated weekly for four or five months, if tolerated by the patient, or until a total of 1 gm. has been given. At the end of this period, the patient will have experienced improvement and the sedimentation rate returned to normal if a favorable response is to be expected. Until recently, the practice has been to discontinue treatment after a remission or after a total of 1 gm. or 1.5 gm. had been given. Such series were repeated at intervals of six to 12 months, or when there was recurrence of manifestations of arthritic activity. During the past three years, as has been stated above, several investigators have given maintenance doses of 50 mg. at three to four week intervals after the initial course. The author has followed this program without observing toxic manifestations, and with results which thoroughly endorse such a practice. Some have recommended a weekly dose of 100 mg. when the response to the usual 50 mg. has not been favorable, but it seems likely that the larger amount will likewise be disappointing. If there is no evidence of improvement after five months of therapy, it is probable that its continuance is useless.

After treatment has been in progress for six to 15 weeks, some change in symptoms and signs of rheumatoid arthritis may be expected if the patient is going to respond. First, there is relief of pain while at rest, then relief on movement. Soon the requirement of salicylates will be voluntarily reduced by the patient. Greater motion is possible and joint swelling becomes less. The general condition of the patient improves, the appetite is better and there is increased strength, and those who have had a bed and wheelchair existence may move about with a crutch, a cane or no support at all.

The reported results of the treatment of rheumatoid arthritis with gold salts have varied greatly, according to different investigators. Forestier [7] in 1935 reported that 70 to 80 per cent of 550 cases had "responded favorably." Cecil [16] et al., in 1942, reported the treatment of 245 patients, 207 with Myochrysine, 40 with Solganal-B oleosum and three with gold sodium thiosulfate. (Some patients received more than one gold salt.) There was a complete remission in 31 per cent, great improvement in 35 per cent, moderate improvement in 20 per cent and no improvement in 14 per cent. Best results were obtained in patients treated early. One-third of the patients with complete remissions and one-half of those greatly improved had recurrences within six months to five years. A second course of treatment again produced a remission in only 50 per cent of those who had had a relapse.

Many other observers have had similar or less satisfactory results, but Short [17] in 1942 observed significant improvement in only six of 31 patients,

three of whom later had relapses. Hench [18] in 1949 said "Chrysotherapy will induce *striking* remissions in only about 10 or 15 per cent of cases." It seems likely that some of these discrepancies may be bridged by the realization that different investigators used different criteria of improvement, some emphasizing objective, others subjective manifestations.

The author has treated 26 patients with Myochrysine during the past eight years, the weekly doses during the first five years being 100 mg., during the past three years, 50 mg. Results have been equally satisfactory with the smaller dosage, and manifestations of toxicity have been less frequent.

Two of the 26 patients have shown no evidence of improvement. The first was 62 years of age and had had arthritis for 12 years, the disease having begun after a thyroidectomy for hyperthyroidism. There was evidence of extensive anatomic change within and about the joints. Little subjective and no objective improvement occurred. The other failure was that of an obese woman, 32 years of age, who worked at a bar where it was necessary for her to spend a great deal of time with her hands in cold water and often to perform arduous physical work. There were few joint manifestations, but pain, swelling and tenderness were conspicuous, apparently involving the fibrous tissue over muscles, tendons and joints. Many subcutaneous nodules were present about the wrists and on both surfaces of the forearms and on the anterior tibial regions. Biopsy of one of those lesions was reported as "compatible with a rheumatic lesion." It is interesting to speculate whether this patient would have responded to gold had she been able to avoid the traumatic factors described above.

Another woman patient, 40 years of age, had an almost identical picture, and an associated upper respiratory infection with blepharitis and conjunctivitis. After 14 weekly injections of Myochrysine the rheumatic manifestations subsided, but the patient had developed a patchy pruritic rash. This complication responded to discontinuance of gold and to conservative local therapy. After two years, mild manifestations recurred; they responded—fortunately—to six weekly gold injections, because at the end of this period the rash had recurred. Treatment was of course terminated, and a second remission has lasted 22 months.

Another especially interesting case is that of a woman, 61 years of age, who was sent to me with a suspected diagnosis of lymphoma. There were rheumatoid arthritis of several years' duration, marked general glandular enlargement, palpable spleen, leukopenia, anemia and weight loss. These criteria for the diagnosis of Felty's syndrome were present, and biopsy of a lymph node showed "simple follicular hyperplasia." General constructive measures, iron and Myochrysine have brought almost complete relief of pain, reduction in joint swelling, greater mobility, gain in weight, normal blood picture and regular attendance at work. The spleen is not palpable at present, but little change in glandular enlargement has been noted. After

14 weeks of gold administration, a rash appeared which involved the scalp, forehead and eyelids, and resembled seborrheic dermatitis. It responded to conservative local therapy and omission of specific treatment for four weeks. Before treatment this patient had had a scant albuminuria, which has now disappeared.

The remaining 22 patients will not be discussed individually, but all have evidenced improvement. Five with symptoms of short duration have been maintained in complete remission during the past two years by monthly intramuscular injections of 50 mg. of Myochrysine, with no evidence of toxic signs. Seventeen patients whose joint changes were further advanced obtained much relief and were able to lead happier, more optimistic lives during the period of observation. Those patients with significant nutritional abnormality or anemia have been benefited in these respects, although dietary, vitamin and iron therapy probably contributed toward attaining this result. Skin rashes necessitated permanent discontinuance of gold in four patients, and relapses have occurred in three of these after periods of seven months to two years.

No serious toxic manifestation has been encountered. A mild diarrhea, apparently secondary to irritation of the intestinal mucosa, has occurred frequently but has subsided when treatment was omitted for three weeks and, curiously, has never recurred. Forty per cent of these patients had at some time a mild albuminuria, which disappeared while treatment was continued. No microscopic hematuria has been noted. During the period when the weekly dosage was 100 mg., dermatitis was a more disturbing factor than during the past three years, when the weekly dosage has been 50 mg. This suggests that the quantity given, as well as drug idiosyncrasy, is a factor in producing the skin rashes.

The prevention of serious toxic reactions during administration of gold salts depends upon the vigilance of the physician. Before each weekly injection, there must be observation of the skin for the presence of a rash or purpuric spots, and of the mouth for stomatitis. The patient must be questioned specifically as to whether there are gastrointestinal disturbances, especially diarrhea. The latter is usually evanescent, subsides with omission of gold for three weeks, and usually does not recur when treatment is reinstituted. It should be recalled that there have been rare reported instances of a secondary fatal ulcerative colitis.

The skin rash is usually mild and pruritic, and it subsides with conservative local measures and omission of gold. Exfoliative dermatitis has been observed but is rare. Hepatic damage has been reported infrequently, but in many instances it has not been possible to eliminate completely other etiologic factors. Doyle and Cannon [19] recently reported a case of severe polyneuritis follwing 900 mg. of Myochrysine for rheumatoid arthritis. Response to conservative management was rapid and complete. These authors quote Sunderlin as stating that complications involving the nervous

system are not infrequent and may be severe, affecting the brain, spinal cord or peripheral nerves. This experience seems to have been most unusual, as the literature contains few references to this type of reaction. The author saw one patient with a mild peripheral neuritis who had been treated elsewhere with a gold salt as well as an arsenic compound.

The urine should be examined weekly for the presence of albumin or microscopic hematuria. Evidence of the latter constitutes an indication for omission of treatment, but the presence of minute amounts of albumin does not, unless it tends to be increasing. As stated above, the slight albuminuria nearly always disappears when treatment is continued. It is of interest that one of the author's patients, before treatment, had a slight albuminuria which subsided after several weeks of gold administration.

Dr. Samuel R. Revell * reports that two patients developed marked proteinuria (one massive, with reduction in total plasma proteins) after the completion of a second course of Myochrysine, approximately one year having intervened between the two courses, each of which totaled less than 1 gm. Neither of these patients had any manifestations of renal disorder during treatment. All evidence of renal dysfunction had returned to normal within nine months in the patient who had had massive proteinuria, but the other patient could not be followed. The course of events in these two patients is somewhat disturbing and warrants prolonged observation of patients who have received gold salts. It is interesting to speculate as to whether this will occur with patients who are maintained uninterruptedly on gold therapy by monthly booster injections.

Hematologic reactions constitute some of the more severe toxic manifestations of gold salt therapy and include granulocytopenia, thrombocytopenia and aplastic anemia, complications which I have not observed. Whereas these disorders are rare after chrysotherapy, they are serious; thrombocytopenia is the most frequent, and aplastic anemia has the poorest prognosis. Aplastic anemia following gold administration has proved fatal in approximately 75 per cent of patients. In 1950, Marriott and Peters [20] presented an interesting discussion of blood dyscrasias secondary to administration of gold salts and reported a case of hypoplastic anemia following its use. The patient did not respond to conservative treatment but did respond to splenectomy and has remained entirely well for three years. It is important to realize that such serious damage to hematopoiesis may occur, and to take every precaution to avoid it. This entails the determination, once every two weeks, of the hemoglobin and total leukocyte and differential counts. In addition, one should make careful inspection of the stained blood smear and blood platelet count if there is reason to believe the platelets are not abundant. Significant deviation from the normal in any of these studies, as well as a tendency to eosinophilia, is to be considered a danger signal and warrants discontinuance of the gold com-

* Personal communication.

pound and further observation. If there is positive evidence of hematologic damage and improvement does not occur promptly, British Anti-Lewisite (BAL) should be administered without delay. This may prevent irreparable bone marrow damage, whether the damage be a direct effect of the gold upon the marrow or mediated through a hormonal influence of the spleen. This latter hypothesis may be considered because gold accumulates selectively in the spleen, presumably in the reticuloendothelial tissue.

The mechanism whereby these toxic reactions are produced is poorly understood. It is believed that both idiosyncrasy and total gold content of the tissue are contributing factors. Freyberg [21] et al. knew that gold appeared in the blood as gold proteinate, and in 1944 he suggested that this compound might be allergenic in persons in whom toxic manifestations occurred. Libenson [22] thought that toxicity might result from the inactivation of sulfhydryl groups in enzyme proteins of tissues by gold, an effect observed with other heavy metals. Block [13] et al. suggested that the beneficial influence of BAL, in combating the toxicity of gold compounds, could be explained by its ability to sever the gold-protein union. This is accomplished because BAL apparently competes effectively, for the gold, with sulfhydryl groups of various tissue proteins. Thus the early employment of BAL should reduce materially the frequency and severity of toxic reactions secondary to gold therapy.

Summary

Gold salts exert a favorable influence upon the course of rheumatoid arthritis. The basis for this conclusion has been presented. A brief review of the development of gold therapy has been given, as well as a discussion of results obtained by many investigators during the past 20 years. The author's results over the past eight years have been related. Emphasis has been placed upon careful selection of patients, small dosage of gold and weekly observation for manifestations of toxicity. Reference has been made to various theories as to the mechanisms whereby gold produces therapeutic effects and, on the other hand, toxic manifestations. BAL should be employed early for the more serious of these toxic reactions. Finally, it may be that further studies in the realm of hormones, such as ACTH and cortisone, will lead to discoveries which will prevent or cure rheumatoid arthritis. Such a goal has not yet been attained, and it is believed that chrysotherapy deserves early consideration in the management of a patient with rheumatoid arthritis.

Addendum

Since this paper was submitted for publication, three of the patients, identified in the tabulated summary by an asterisk, have had reactions to gold.

Patients R. R. and E. K. developed slightly troublesome dermatitis with pruritus and slight exfoliation. The lesions in the first patient were limited

BRIEF SUMMARY OF CASES

Name	Age in Years	Sex	Duration of Illness	Extent of Disease	Dosage of Gold	Duration of Gold Therapy	Reactions	Subjective Improvement	Objective Improvement
K. H.	62	F	12 years	4 plus	100 mg.	8 mos.	Transient slight albuminuria and diarrhea	?	None
G. M.	58	M	1 year	3 plus	100 mg.	5 mos.	Moderately severe dermatitis. Eosinophilia of 12%—disappeared with cessation of Myochrysine	2 plus	2 plus
E. E.	31	F	5 years	1 plus	100 mg.	4 mos.	Mild diarrhea	2 plus	?
E. C.	47	F	14 years	4 plus	100 mg.	4 mos.	Mild dermatitis; Myochrysine discontinued	2 plus	Plus
M. B.	42	F	7 years	2 plus	100 mg.	4 mos.	Transient slight albuminuria	4 plus	Plus
I. Z.	32	F	14 mos.	2 plus	100 mg.	5½ mos.	Mild dermatitis; subsided after Myochrysine was omitted for 4 weeks	?	None
C. R.	40	M	14 years	3 plus	100 mg.	6 mos.	Transient slight albuminuria	Plus	Plus
L. R.	52	F	6 years	3 plus	100 mg.	4 mos.	None	2 plus	Plus
L. W.	38	F	4 years	2 plus	100 mg.	4 mos.	Transient slight albuminuria	3 plus	2 plus
E. C.	46	F	16 years	4 plus	100 mg.	4 mos.	None	Plus	Plus
R. W.	38	M	8 mos.	1 plus	100 mg.	5½ mos.	Transient mild dermatitis and albuminuria; Myochrysine discontinued when dermatitis recurred	4 plus	4 plus
W. L.	35	M	3½ years	2 plus	50 mg.	3 mos.	None	2 plus	Plus
(1946) R. L. (1948)	40	F	4 weeks	2 plus	100 mg.	14 weeks	Mild dermatitis. Transient diarrhea	4 plus	4 plus
	42	F	6 weeks	Plus	50 mg.	6 weeks	Mild dermatitis. Eosinophilia 7%. Myochrysine discontinued	4 plus	4 plus
H. M.	42	M	4 years	2 plus	100 mg.	4 mos.	Transient albuminuria. Slight granulocytopenia	2 plus	Plus
H. J.	54	F	12 years	4 plus	50 mg.	19 mos.	Transient albuminuria	Plus	Plus
R. K.	40	F	1 year	1 plus	50 mg.	20 mos.	None	4 plus	4 plus
B. H.*	63	F	11 years	3 plus	50 mg.	4½ mos.	Transient albuminuria	3 plus	2 plus
B. W.	61	F	14 years	3 plus (Felty's)	50 mg.	20 mos.	Seborrhea-like dermatitis of one month's duration; no recurrence. Eosinophilia 14%	3 plus	2 plus
R. R.*	47	F	13 years	3 plus	50 mg	24 mos.	Transient albuminuria	4 plus	2 plus
D. P.	38	F	8 mos.	1 plus	50 mg.	23 mos.	None	4 plus	4 plus
S. M.	64	F	3 years	3 plus	50 mg.	13 mos.	Transient slight albuminuria. Transient slight granulocytopenia	3 plus	2 plus
G. R.	37	M	7 mos.	2 plus	50 mg.	22 mos.	None	4 plus	4 plus
F. G.	45	F	8 years	3 plus	50 mg.	9 mos.	None	2 plus	Plus
F. Mc.	45	F	6 weeks	1 plus	50 mg.	27 mos.	Mild diarrhea	4 plus	4 plus
E. K.*	68	F	41 years	3 plus	50 mg.	12 mos.	Transient slight albuminuria	3 plus	2 plus
S. L.	57	M	5 mos.	2 plus	50 mg.	26 mos.	None	4 plus	4 plus

to the tibial areas, whereas there were small areas of involvement about the upper thighs, perianal area, fingers, eyes and ears of the second patient. The lesions about the eyes and ears improved greatly when the gold frames of this patient's glasses were replaced by plastic ones. The dermatitis responded well to compresses with dilute Burow's solution and boric acid ointment with phenol 1 per cent.

Patient B. H. developed an unusually severe diarrhea (eight to 12 liquid stools daily without mucus or blood), with much tenesmus, lower abdominal cramps and tenderness, accompanied by frequency and urgency of urination. The urine was clear and the stools contained no blood by gross examination; chemical tests of the stool were very faintly positive for blood. These manifestations subsided gradually during six weeks of symptomatic treatment. At no time did it seem necessary to use BAL.

Whereas the patients are fearful that there soon may occur an exacerbation of arthritis, both patients and author agree that re-institution of gold therapy is contraindicated in these cases.

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THE ORAL ADMINISTRATION OF VITAMIN B_{12} IN TROPICAL SPRUE *

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Three years ago, Shorb [1] discovered a new factor in refined liver extracts that was highly potent in promoting growth of the microörganism *Lactobacillus lactis* Dorner. Using the microbiologic method of Shorb, Riches [2] et al. isolated a pure crystalline compound from liver and designated it vitamin B_{12}. West [3] proved that this substance possessed the property of inducing a hematopoietic response in patients with pernicious anemia in relapse. At about the same time, Smith [4] in England announced the isolation of a factor apparently identical to vitamin B_{12}.

Chemistry of Vitamin B_{12}

Crystalline vitamin B_{12} occurs as dark red needles. On a weight-for-weight basis, it appears to be the most active of any known vitamin. Its chemical structure is yet not known, but it is known to contain cobalt in the molecule. The parenteral use by West [5] of cobalt acetate or chloride in patients with pernicious anemia has given negative results. Smith [6] reports that cobalt makes up 4 per cent of the dried weight of vitamin B_{12}, and estimates its molecular weight to be within the range of 1,550 to 1,750, suggesting a complex molecule. Spectrographic examinations of vitamin B_{12} show the presence of phosphorus and nitrogen but no sulfur. The analytic study of this vitamin by Smith reveals that the molecule contains three atoms of phosphorus. The red color of the crystals is due to the presence of cobalt. These crystals darken to black at about 210 to 220° C., but they do not liquefy below 300° C.

Source of Vitamin B_{12}

This vitamin is presumably found in many foods. The content of vitamin B_{12} in liver is small, rendering this source unsuitable for its commercial preparation.

Riches and associates [2] found a high content of this vitamin in cultures of *Streptomyces griseus*. At the present time vitamin B_{12} is being obtained

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from this source. The vitamin obtained from this fungus is chemically and physically identical with that obtained from liver. It also has the same growth-promoting potency for *Lactobacillus lactis* Dorner and *Lactobacillus leichmannii*. The response of patients with pernicious anemia to vitamin B_{12} obtained from either source seems to be identical.[8]

Clinical Uses

Several investigators, like West,[8] Bethell,[7] Hall and Campbell[9] and others, have shown that the parenteral use of vitamin B_{12} induces a hematopoietic response similar to that produced by liver extract in cases of pernicious anemia in relapse. The neurologic manifestations of those patients treated with vitamin B_{12} are relieved in the same manner as with liver extract.

Beneficial results from parenteral administration of vitamin B_{12} in tropical and nontropical sprue have been reported by Spies, Suárez and associates.[10]

Bethell and associates[7] report beneficial results when vitamin B_{12} is administered parenterally to patients with nutritional macrocytic anemia.

Parenteral Dosage

The parenteral dosage is not definitely known. In this respect Spies states: ". . . perhaps the average patient with pernicious anemia in relapse or with tropical or non-tropical sprue, will respond maximally to 100 μ gm. or less intramuscularly. The great majority of patients seem to respond minimally to from 8 to 10 μ gm. intramuscularly." The suggested average dosage for patients with pernicious anemia in relapse is 15 μ gm., once or twice a week intramuscularly until remission occurs. The maintenance dosage is 15 μ gm. every two to four weeks given intramuscularly.

Oral Use of Vitamin B_{12} in Pernicious Anemia

The oral administration of vitamin B_{12} has been studied by several investigators in untreated cases of pernicious anemia. Castle and associates[11] administered daily by mouth for a 10 day period 5 μ gm. of vitamin B_{12} (Merck), dissolved in 125 to 150 c.c. of physiologic saline solution, to four patients with untreated pernicious anemia. During a second 10 day period, the same amount of vitamin B_{12} was given simultaneously with 150 c.c. of normal human gastric juice that had been previously neutralized with sodium hydroxide. Particular attention was paid to administering the gastric juice 10 hours after the heaviest meal and four hours after the evening meal. The gastric juice alone had no hematopoietic action. In each case, when vitamin B_{12} and gastric juice were given simultaneously, a reticulocyte response was obtained that was accompanied by an increase in the red blood

cells in three cases. In two cases the reticulocyte peaks were not marked. No hematopoietic effect whatsoever was noted when the vitamin B_{12} was given alone or 12 hours after administration of gastric juice. Clinical improvement did not appear until the reticulocyte response occurred following the combined use of vitamin B_{12} and gastric juice.

They concluded that the hematopoietic activity in pernicious anemia of orally administered vitamin B_{12} is potentiated by the simultaneous administration of normal human gastric juice, but, as with liver extract, is not so great as the activity of vitamin B_{12} when given parenterally. They suggest that the food (extrinsic) factor may be identical with or closely related to the antipernicious anemia principle of liver, which is in itself presumably identical with vitamin B_{12}. They also point out that the gastric (intrinsic) factor is necessary for the optimal utilization of the relatively small amounts of vitamin B_{12} used, or of clinically related substances present in various foods.

Hall and Campbell,[9] from the Mayo Clinic, have also studied the effect of oral administration of vitamin B_{12} in pernicious anemia. Pooled gastric juice containing more than 30 degrees of free hydrochloric acid was obtained from patients with uncomplicated duodenal ulcer or with functional gastrointestinal disturbances. The pooled specimens of gastric juice were passed through a Berkefeld filter and stored in an icebox for less than 96 hours. Before the gastric juice was administered it was neutralized with sodium hydroxide.

Four patients with pernicious anemia in relapse were studied. The medication was administered not less than one hour before the first meal of the day. Meat and eggs were withheld from the morning meal, but the other meals had unrestricted amounts of proteins. The same source and amount of vitamin B_{12} as in Castle's patients were used. These investigators obtained optimal responses in two of the four patients studied, a result much better than that obtained by Castle. They explained this difference on the basis of the different time relation between the medication and the ingestion of food, or possibly of the nature of their noon meal. The fact that the source of their gastric juice was different from that used in Castle's study may have had something to do with the difference in the results obtained.

They concluded that there is need of further studies on the oral use of vitamin B_{12}, given in larger doses, before any conclusions are drawn about the value of its oral administration. These investigators agree with Castle that gastric juice potentiates the hematopoietic effect of orally administered vitamin B_{12}, but that the vitamin alone, in the doses used, failed to produce any beneficial effects. They established that the minimal daily quantity of gastric juice needed to potentiate an optimal hematopoietic response from 5 μ gm. of vitamin B_{12} when given by mouth to patients with pernicious anemia in relapse lies between 25 and 150 c.c.

Oral Use of Vitamin B_{12} in Sprue

In this study vitamin B_{12} * was administered to 10 patients with active sprue who had definite macrocytic anemias. Ten patients received vitamin B_{12} alone by mouth. Three patients of this group received vitamin B_{12} and gastric juice simultaneously.

Seventy-five to 150 c.c. of gastric juice of more than 30 degrees of free hydrochloric acid were used. It was obtained from patients with uncomplicated duodenal ulcers. The medications were given while the patient was fasting, and the next meal was taken four hours later.

All patients were placed on a "preliminary sprue" diet on admission to the hospital. This diet contains 3,718 calories per day and has 134.5 gm.

Table I

Name Age Sex Color	Type of Medication	Hemoglobin %			R.B.C. × 10^6			Reticulocytes %			M.C.V. cu. μ		
		Initial	6–8 days	12–14 days	Initial	6–8 days	12–14 days	Initial	Maximum 6–8 days	12–14 days	Initial	6–8 days	12–14 days
1. R. R. 26 yrs. Female White	30μ gm. B_{12} p.o. 15μ gm. B_{12} p.o.* Folic acid, 10 mg. tid p.o.	47.5 42.5 37.5	47.5 45 45	42.5 41.2 50	2.15 2.04 1.91	2.00 2.43 2.64	2.04 2.22 2.9	.4 .6 .6	1 2.6 8	.6 0 3.4	109 95 89	115 83 100	95 90 100
2. F. M. 42 yrs. Male White	50μ gm. B_{12} p.o. 450μ gm. B_{12} p.o. Folic acid, 15 mg./d. p.o.	50.2 55 50	50.2 55.2 66.1	55 55.2 72	2.12 2.5 2.8	2.42 3.33	2.5 3.12 3.6	.8 9.8 2.0	11.8 5.4 24.2	9.8 1.8 4.2	113 91 78	90 88 99	91 86 100
3. E. V. 23 yrs. Female White	60μ gm. B_{12} p.o.	62.5	70	55	2.40	2.78	2.29	.2	2.2	1.6	113	111	118
4. F. C. 50 yrs. Female White	30μ gm. B_{12} p.o. 100μ gm. B_{12} p.o. 15μ gm. B_{12} I.M.	72.5 75 65	75 70 70	75 65 77.5	2.70 2.85 2.56	2.85 2.72 2.7	2.85 2.56 2.97	.6 .8 .6	.8 .6 3	.8 .6 1	125 114 112	114 118 122	114 112 124
5. R. R. 68 yrs. Male White	50μ gm. B_{12} p.o. 50μ gm. B_{12} I.M.	68 66	71 66.1	71 74.1	3.2 3.06	3.37 3.60	3.36 3.68	.6 2	1.4 14.8	4.8 2.0	100 98	97 94	95 86

* Dose was repeated twice with the same results.

of protein, 568.5 gm. of carbohydrate and 102 gm. of fat. The diet allows for six ounces of milk a day, and 20 gm. of animal protein were given once or twice a week. The remainder of the protein used was obtained from vegetable sources.

The gastric juice was neutralized with sodium hydroxide before it was used. All the cases studied had free hydrochloric acid in their gastric juice with histamine stimulation except case 7. The hemoglobin, red blood cells and mean corpuscular volumes were checked twice a week. Reticulocyte counts were done every day. Of the 10 cases receiving oral vitamin B_{12} alone, two cases received larger doses for longer periods of time.

* Obtained mainly from the Squibb Laboratories.

Results from the Oral Administration of Vitamin B_{12} in Sprue

In table 1 the results of the oral administration of vitamin B_{12} alone are compared with the results obtained from the use of either folic acid or vitamin B_{12} intramuscularly.

Oral vitamin B_{12} alone was given to 10 patients. Small single doses of 15 to 50 μ gm. of vitamin B_{12}, given to eight patients, produced an optimal response in one (case 2), a suboptimal response in five (cases 1, 3, 5, 7 and

Table II

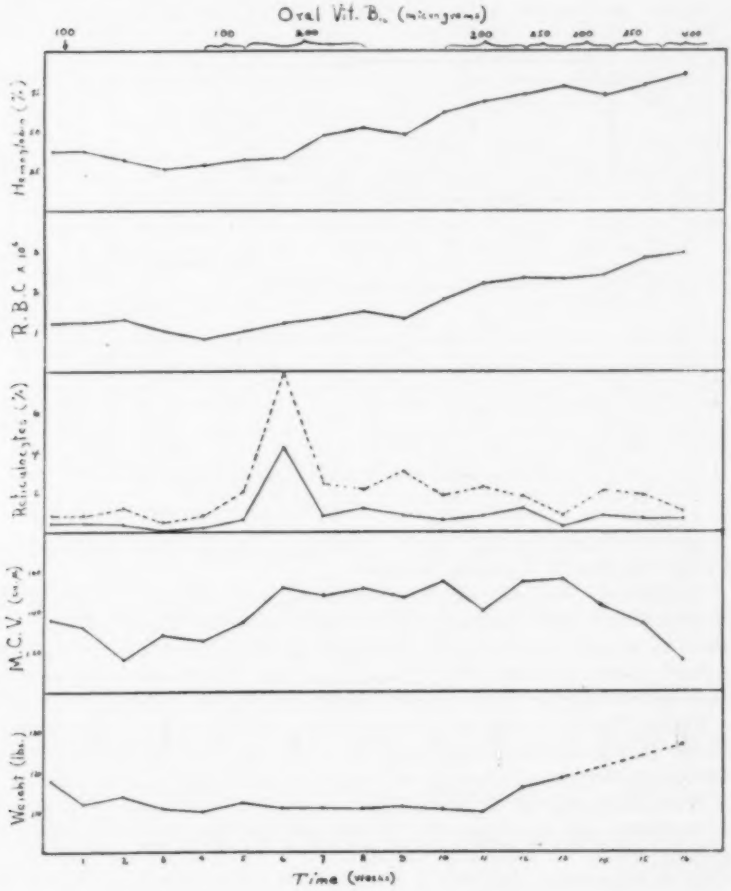
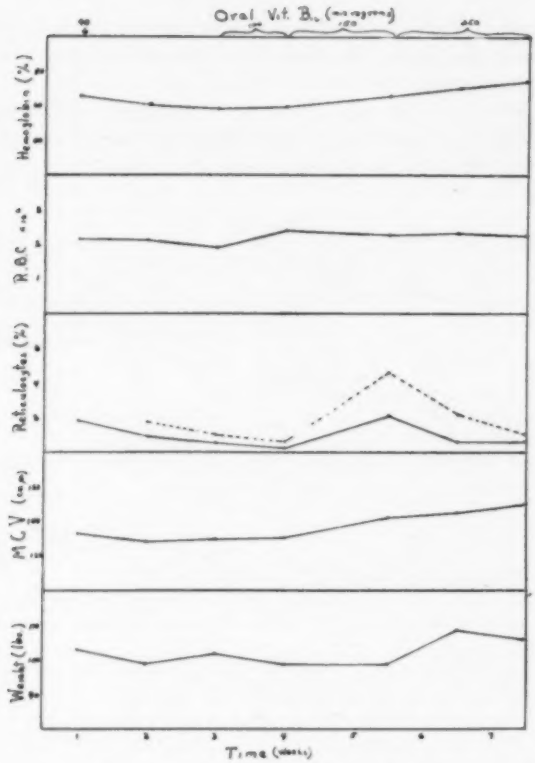


TABLE III



8), and no response in two (cases 4 and 6). Case 4 responded poorly to 15 μ gm. of vitamin B_{12} intramuscularly.

When larger single doses (90 to 450 μ gm.) of vitamin B_{12} were given orally to four patients, a suboptimal response occurred in one (case 2), as shown by an increase in the red blood cell count. There was no response in three (cases 4, 9 and 10). Either folic acid or intramuscular vitamin B_{12} produced superior results when compared to the oral vitamin B_{12} used.

Tables 2 and 3 show the effect of oral administration to two patients of large daily doses of vitamin B_{12} alone. When multiple daily doses of 100 to 400 μgm. were used, a suboptimal response was obtained in each case.

A reticulocytosis developed in each case when the dose had been increased to 150 to 200 μgm. of vitamin B_{12} per day and had been used for a period of seven days.

In the first case (table 3), it took 16 weeks for the hemoglobin to in-

crease from 35 to 85 per cent and for the red blood cell count to increase from 1.3 to 3 millions per cu. mm. Clinical response as shown by disappearance of the glossitis and diarrhea occurred after 12 weeks of medication.

In the second case (table 3), after six weeks of medication the hemoglobin increased from 64 to 72 per cent, and the diarrhea and glossitis disappeared.

Table 4 compares the hematopoietic action of vitamin B_{12} given alone with that of simultaneous administration of vitamin B_{12} and gastric juice.

A suboptimal response was obtained in two cases (cases 7 and 8), and no response developed in the third (case 6). This "failure case" was treated twice, using 90 and 150 c.c. of gastric juice, without any response,

TABLE IV

Name Age Sex Color	Type of Medication	Hemoglobin %			R.B.C. × 10^6			Reticulocytes %			M.C.V. cu. μ		
		Initial	6–8 days	12–14 days	Initial	6–8 days	12–14 days	Initial	Maximum 6–8 days	12–14 days	Initial	6–8 days	12–14 days
5. A. L. R. 21 yrs. Male White	30μ gm. B_{12} p.o.	32.5	27.5		1.51	1.07		.2	1		100	120	
	30μ gm. B_{12} + 90 c.c. of gastric juice	27.5	26.2	23.7	1.07	.97	1.02	1	.4	.2	120	113	120
	30μ gm. B_{12} + 150 c.c. of gastric juice	17.5	13.7		.92	.58		0	.4		111	110	
	15μ gm. B_{12} I.M.	13.7	30		.58	1.00		.4	4.8		110	120	
6. C. Q. R. 28 yr. Male White	1μ gm. B_{12} p.o. daily for 7 days	12.5	7.5		1.10	.79		1.6	1.6		81	85	
	30μ gm. B_{12} p.o.	12.5	15		1.12	1.20		1.2	2.8		81	75	
	30μ gm. B_{12} + 75 c.c. gastric juice	16.2	22.5	22.5	1.19	1.30	1.30	.4	4.2	.6	72	81	84
	15μ gm. B_{12} I.M.	16.2	40		.78	1.90		1.0	5.0		100	110	
7. C. R. 60 yrs. Female White	30μ gm. B_{12} p.o.	22.5	26.2	21.2	1.04	1.00	1.00	.8	1.6	.8	120	100	90
	30μ gm. B_{12} + 75 c.c. gastric juice	20	20	16.2	1.00	1.00	.72	.6	3.8	2.2	90	90	128
	60μ gm. B_{12} p.o.	16.2	21.2		.72	1.01		2.2	3.0		128	90	
	60μ gm. B_{12} + 100 c.c. gastric juice	24.2	25	26.2	1.13	1.00	1.02	.6	2.0	.2	90	120	110
	15μ gm. B_{12} I.M.	20	33.7	47.5	.90	1.70	1.82	.8	37.2	1.8	100	105	133

* Gastric juice was obtained from patient with duodenal ulcer.

while intramuscular administration of vitamin B_{12} produced an adequate increase in the reticulocyte count, hemoglobin and red blood cell count.

Gastric juice appeared to have potentiated the hematopoietic action of oral vitamin B_{12} in two cases (7 and 8).

CONCLUSIONS

1. Vitamin B_{12} alone, given by mouth, has a definite but limited hematopoietic activity in sprue.

2. Gastric juice potentiated the hematopoietic activity of orally administered vitamin B_{12} in two cases out of three.

3. Small single doses of vitamin B_{12} (15 to 50 μ gm.), given alone by mouth, failed to induce a hematopoietic response in two cases out of eight

that were treated. Of these eight cases, one had an optimal response and five had suboptimal responses.

4. Large single doses of vitamin B_{12} (90 to 450 μ gm.) failed to induce a response in three out of four cases when given alone by mouth.

5. Large multiple daily doses of 100 to 400 μ gm. of vitamin B_{12} given alone by mouth to two patients induced a suboptimal response in each case. Definite clinical improvement occurred in six weeks in one case and in 12 weeks of treatment in the other case.

6. In sprue it appears that the approximate minimal dose of vitamin B_{12} needed to produce an appreciable reticulocytosis and definite *clinical* improvement when given alone by mouth is between 150 and 200 μ gm. daily for at least two to three weeks or longer.

7. Fifteen milligrams of folic acid by mouth daily, or 15 micrograms of vitamin B_{12} intramuscularly, are more potent hematopoietic agents than the oral administration of vitamin B_{12} in the doses used in this study, either alone or mixed with gastric juice.

8. The potentiating hematopoietic action of gastric juice on orally administered vitamin B_{12} to patients with sprue seems to be inferior to the results obtained with pernicious anemia by Castle or by the Mayo Clinic group, even though larger doses were used. This difference may have been due to the difference in the source of the vitamin B_{12}. In this study the Squibb's preparation was used in eight cases, while Castle [11] and Hall and Campbell [9] used vitamin B_{12} supplied by Merck laboratories. Another possible explanation for this difference in response in sprue might be that, in this condition, even though we might have enough intrinsic factor, the intestinal absorption of the extrinsic factors or the antipernicious anemia factor (vitamin B_{12}) is impaired.

9. At the present time, the oral use of vitamin B_{12} in sprue is not the most efficient or practical way to treat this disease.

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THE SYNDROME OF THROMBOSIS OF THE POSTERIOR INFERIOR CEREBELLAR ARTERY: A REPORT OF 28 CASES *

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The syndrome resulting from occlusion of the posterior inferior cerebellar artery (PICA) was defined clearly by Wallenberg in 1895.[1] Typically there is, without loss of consciousness, a sudden onset of vertigo, falling, unilateral ataxia, vomiting, diplopia, paresthesias, dysphagia and dysphonia. Horner's syndrome, cerebellar signs, unilateral palatal paralysis, ipsilateral loss of pain and temperature perception of the face and similar sensory impairment on the contralateral side of the body are observed.

In 1946 Louise-Bar,[2] in an elaborate review of the literature of this entity, listed 240 references and presented six cases. Most of the clinical reports deal with one or two cases, and a few describe six or eight cases. The small number of cases reported is not in accord with the opinion, frequently expressed, that the lesion is not rare. Levine et al.,[3] for example, found three cases at Beth Israel Hospital in Newark in a single year. Brown [4] stated that he has seen 15 cases in two years. While there is general agreement on the typical clinical manifestations of the syndrome, there has been no attempt to estimate the frequency with which the various symptoms and signs are present.

We were prompted to undertake this study because we have had available a considerably larger group of patients than has previously been described in one report.

The Clinical Material

This report describes 28 cases seen at the Cook County Hospital from 1938 to 1949. Twenty cases were observed in 1948 and 1949, many of which we examined, while eight were seen by others in the previous 10 year period. The patients seen in the earlier period were all on the neurology service, whereas in most of the recent cases the diagnosis was made on the medical wards. In most instances the diagnosis was confirmed by consultants from the Neurology Department. We attribute the apparent increase in incidence to the increased awareness on the part of the general medical staff of the clinical features of the syndrome.

We were able to reexamine 10 patients from six to 24 months after their acute episodes and to obtain some information on two others, one of whom died eight years after his occlusion.

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Age, Sex, Race Distribution. As shown in table 1, 86 per cent of the patients were between the ages of 40 and 69. This corresponds closely to the age incidence of the other more common forms of cerebral vascular thromboses as seen at Cook County Hospital. Sixteen, or 57 per cent, of our patients were Negroes and the remainder were white.

Associated Diseases. Sixteen patients were found to have hypertension, and in two additional cases there was a history of hypertension prior to the stroke. In 11 cases there were findings of early to moderate retinopathy.

In 18 cases, reports of the Kahn or Wassermann reactions or both were available. All were negative. In 13 of these patients the Wassermann reaction of the spinal fluid was negative, and in one case it was positive. In three additional cases there was a history of treated syphilis.

There was one diabetic in the entire group.

TABLE 1
Age and Sex Incidence

Age	Male	Female	Total
20–29	0	1	1
30–39	0	0	0
40–49	4	4	8
50–59	4	2	6
60–69	9	1	10
70–79	3	0	3
Total	20	8	28

In our presentation, *incidence is always expressed with reference to the number of cases in which the presence or absence of the sign or symptom is unequivocally recorded.* In relatively few instances were the records incomplete with regard to the important observations.

SYMPTOMS

The incidence of the various symptoms is listed in table 2. It is clear from these data that certain symptoms occurred regularly. We wish to emphasize, however, that there was great variation in the relative severity of the various complaints, which led to difficulty in diagnosis in some cases.

Prodromata. Three patients complained of dizziness and headache during a period of up to two weeks before the stroke. These complaints occurred suddenly once or twice and lasted from several minutes to an hour. In the remaining cases no prodromal symptom was described.

Onset. The onset was acute in 27 cases, with sudden dizziness and headache. In one otherwise typical case, the onset was gradual over a period of several hours. In many cases paresthesias were noted immediately, and in two instances vomiting occurred at once. The other symptoms

usually were not perceived for several hours, and some complaints, often hiccough, did not appear until several days later.

Vomiting. Vomiting occurred in 20 of the 28 cases, or 71 per cent. It was nonprojectile in character and often was not related to meals. In some cases this symptom was of such severity that parenteral fluids were required for several days. In all cases the vomiting gradually became less frequent and did not recur after the second week.

Dysphagia. Twenty patients, or 80 per cent of 25 cases, had dysphagia. Most patients had complete recovery of the ability to swallow, but several required tube feedings for as long as a month. One patient, six months after her stroke, often has sufficient dysphagia to require self-administered tube feedings. Milder degrees of this complaint were present in three cases for from six to 16 months.

TABLE II
Symptoms

Complaint	Present	Denied	Not Clearly Recorded
Acute onset	27	1 (subacute)	0
Vomiting	20	8	0
Dysphagia	20	5	3
Giddiness	23	2	3
Vertigo	22	1	5
Falling	14	11	3
Paresthesias	21	2	5
Dysphonia (including hoarseness)	19	5	4
Hiccough	14	7	7
Diplopia*	16	4	6
Motor weakness	20	2	6
Headache	16	5	7

* Two patients were blind prior to the stroke.

Dizziness was present in 23 of 25 patients or 92 per cent. This complaint, differentiated from true vertigo, rarely was troublesome for more than several days. However, *vertigo,* which occurred with about the same frequency, was incapacitating in several cases. In one otherwise typical case, this complaint kept the patient from getting out of bed for two years. A history of *falling* was obtained in 14 cases (58 per cent) and denied in 10 cases. In three of the 14 patients who fell, there was no specific statement in the record regarding the presence or absence of vertigo. In all of the 11 patients who fell, where mentioned, vertigo was present. Several of the patients who fell did not have motor symptoms or paresis. The correlation of falling with vertigo and poorer correlation with motor symptoms suggest that the falling is on the basis of cerebellar dysfunction. That all patients with vertigo did not fall perhaps could be explained by differences in attempting to walk, presence of supporting objects or persons, etc., as well as by differences in the severity of this complaint. Dizziness was a

persistent complaint in three cases at the time of reëxamination, eight months to two years later. This was severe enough in only one instance to interfere with activity.

Paresthesias were present in 21, or 91 per cent of 23 patients, and were characteristically an early complaint. Four patients had pain in the face either on the side of the lesion or on the contralateral trunk. In four additional cases there was perversion of sensation in the area of diminished pain and temperature sensibility. This consisted of the perception of pain on the application of warm or cool objects to the involved areas, as in patients with thalamic lesions. In all cases, the areas in which any kind of abnormal sensations were felt corresponded anatomically to the areas of diminished pain and temperature perception. At no time did paresthesias require the use of sedatives. This symptom disappeared gradually in some cases, but in seven of the 11 patients examined later the sensation of burning or numbness had persisted for a period of from six months to two years.

Dysphonia was found in 19 cases, or 79 per cent of the 24 satisfactory records. In most instances this consisted of hoarseness, but in several it consisted of slurred speech. Aphonia did not occur. The speech disturbance disappeared entirely except for one patient, whose hoarseness persisted until his death eight years later.

Hiccough occurred in 14 patients, representing 62 per cent of 21 cases. This disappeared in all cases within two weeks, but in a few instances it was very annoying during the first week.

Diplopia. This complaint was mentioned by 16 patients and denied by four, giving an incidence of 80 per cent. Two patients were blind prior to the development of the syndrome. In the patients with diplopia, no paresis of the extraocular muscles was demonstrated. Double vision was distressing to some patients but in others was present only on lateral gaze. In all cases it was of short duration and disappeared completely.

Motor weakness, referring to diminished muscular strength in the extremities of one side, was recorded in 20 (91 per cent) of 22 cases. The weakness was usually mild, and none of the patients had complete paralysis. Slight unilateral motor weakness was described by six of the 11 patients seen on follow-up examination; in three of these instances, slight weakness could be detected clinically, in two cases limited to the hand.

Headache occurred in 16 of 21 patients, or 76 per cent. This had no characteristic location or quality and sometimes required aspirin for relief. The duration was never more than several days.

Neurologic Findings

The consistent widespread neurologic abnormalities, as listed in table 3, result from involvement of the sympathetic centers, sensory nuclei and tracts, cerebellar and vestibular systems, certain cranial nerves and the pyramidal tracts.

Horner's syndrome was found in 24 of 27 cases, or 89 per cent. It regressed slowly, and in six patients it was present at the follow-up examination from six to two years after the episode.

Sensory Nuclei and Tracts Involving Pain and Temperature Perception. Impairment in this modality was shown in the distribution of the ipsilateral trigeminal nerve in 20 of 27 cases, or 74 per cent. In four cases, or 15

TABLE III

Neurologic Abnormalities

	Present	Absent	Not Clearly Recorded
1. Horner's syndrome	24	3	1
2. Impairment of pain and temperature perception			
(a) Ipsilateral face and contralateral trunk	20		
(b) Contralateral face and contralateral trunk	4		
(c) Contralateral trunk only	3		
Total	27		
3. Cerebellar signs (exclusive of nystagmus)	17	7	4
Nystagmus	18	8	2
4. Cranial nerves			
(a) Diplopia	16	4	6*
(b) Facial weakness	19	7	2
(c) Palatal paralysis	19	6	3
(d) Dysphonia (including hoarseness)	19	5	4
(e) Dysphagia	20	5	3
(f) Hiccough	14	7	7
5. Hemiparesis			
(a) Ipsilateral	12		
(b) Contralateral	8		
Total	20	6	2
6. Babinski's sign			
(a) Ipsilateral	5		
(b) Contralateral	6		
Total	11	13	4

* Two patients were blind prior to these episodes.

per cent, there were similar sensory changes in the contralateral distribution of this nerve. However, in all 27 cases the sensory loss on the trunk and extremities was contralateral to the lesion. Thus, although this contralateral sensory impairment in the trunk and extremities was invariable, the impairment of this modality in the face was less consistent both in occurrence and laterality. In the 10 cases in which careful neurologic examina-

tions were repeated from six months to two years after the episodes, we found *persistent sensory changes in nine, or 90 per cent.* In eight patients these consisted of mild to marked impairment of pain or temperature perception or both. This was present on the contralateral side of the trunk and extremities in all cases, and also on the ipsilateral side of the face in three. In one case there was perversion of sensation remaining.

Cerebellar and Vestibular Systems. We did not study the individual cerebellar signs because of the variations in the recording of these tests. However, one or more typical cerebellar signs (other than nystagmus) were described in 17 or 24 cases, or 78 per cent. These signs usually had disappeared by the end of the second week, but slight residuals were found in two cases after six and 13 months.

Nystagmus was demonstrated in 18 of 26 cases, or 69 per cent. This sign is considered separately because in two patients nystagmus was found without cerebellar signs. Also, three patients with cerebellar signs did not have nystagmus. In none of the patients observed later did this sign persist.

Cranial Nerves.

1. *Diplopia* is mentioned in this group for convenience although, as mentioned below, it may not be due to cranial nerve involvement. We have discussed this finding in the section on symptoms.
2. *Facial weakness.* There was no patient with actual facial paralysis. However, weakness of facial muscles or definite flattening of the nasolabial fold was observed in 19 of 26 cases, or 73 per cent. This finding was always ipsilateral. It persisted in five of the cases examined from six to 24 months later.
3. *Palatal paralysis* occurred in 19 of 25 cases, or 76 per cent. This varied from slight to marked, was ipsilateral in all instances and remained in three of the patients observed later.
4. *Dysphonia, dysphagia and hiccough* were considered in the section on symptoms.

Pyramidal Tract. Complete paralysis did not occur. In 20 of the 26 cases, or 77 per cent, there was distinct *weakness* of the extremities on one side. In 12, or 60 per cent of these patients, the weakness was ipsilateral, whereas in the remaining 40 per cent it was contralateral. There was slow restoration of muscular power. In five of the nine cases reëxamined afterward, there was a complaint of unilateral weakness, but this could be demonstrated on testing in only two instances.

Babinski's sign was found in 11 of 24 cases, or 46 per cent. In five instances this sign was present on the side of the lesion, and in six it was contralateral. There was no patient having a bilateral Babinski's sign after the examination on admission. In six of the nine patients in whom both

Babinski's sign and hemiparesis were present, these findings were on the same side, whereas in three instances they were crossed.

Anatomy and Pathophysiology

The PICA is the longest and largest branch of the vertebral artery. It supplies the posterior inferior surface of the cerebellum and the lateral part of the medulla oblongata. This artery anastomoses with its fellow of the opposite side and with a branch of the superior cerebellar artery. As the PICA winds around the medulla it gives off terminal vessels to the retro-olivary area. Since these vessels are end arteries and are the only source of blood supply to this area, occlusion of the PICA will produce softening in the lateral part of the medulla. The occlusion will not affect other regions because the remaining branches are not end arteries.[5]

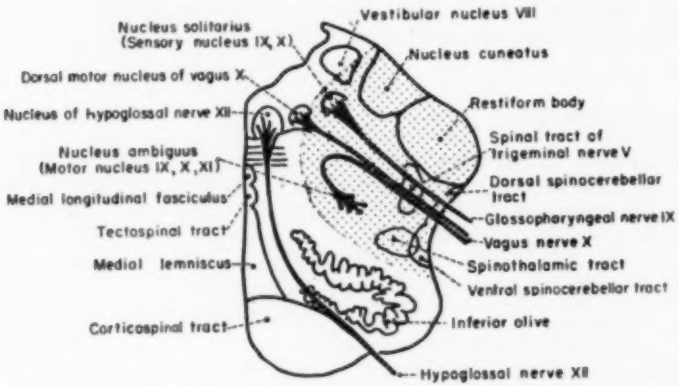

Fig. 1. Cross section of the medulla at mid-olivary level. (Redrawn from Purves-Stewart: The Diagnosis of Nervous Diseases, Ed. 9, 1945, Williams & Wilkins, Baltimore; with permission.)

The medial side of the medulla, which includes the hypoglossal nucleus and nerve, the mesial fillet, the posterior longitudinal bundle and the pyramidal tract, is not affected. This area receives its blood supply from the upper branch of the anterior spinal artery which arises from the vertebral artery.[8]

The lesion produced by the occlusion of the PICA extends from the olivary body in front to the entrance of the restiform body into the cerebellum behind. The level of the middle of the hypoglossal nucleus is the lower limit of the softening, while the upper limit extends to the level at which the restiform body enters the cerebellum.[8] In this area of softening are important sensory and motor nuclei and pathways whose functions become reduced or lost (figure 1). These structures include:

1. Medullary extension of the lateral spinothalamic tract, carrying pain and temperature sensation from the opposite side of the body.
2. Medullary extensions of the anterior and posterior spinocerebellar tracts, carrying deep sensibility impulses to the cerebellum.
3. Descending root and nucleus of the trigeminal nerve, conveying pain and temperature sensation from the ipsilateral side of the face.
4. Nucleus ambiguus, which supplies the striated muscles of the pharynx, larynx and soft palate via the IX and X nerves.
5. Reticular formation, containing the sympathetic pathway from the hypothalamus to the spinal cord, and also the respiratory center.[5]
6. Sensory nuclei of the glossopharyngeal and vagus nerves and the dorsal nucleus of the vagus.
7. Restiform body (inferior cerebellar peduncle).
8. Deiters' (lateral vestibular) nucleus.

Production of Symptoms and Findings

Sensory Disturbances. Loss of pain and temperature sensation on the ipsilateral side of the face occurs in the distribution of the trigeminal nerve because the lesion includes the descending root and tract of this nerve. Paresthesias in this area are explained on the same basis. The other sensory modalities of the face are intact because the chief sensory nucleus in the upper portion of the pons is unaffected. We are unable to explain why in four cases the sensory impairment in the face was contralateral to the lesion. This variation has been observed before.[8] The contralateral paresthesias and sensory loss on the trunk and the extremities result from the interruption of the spinothalamic tract passing through the medulla. Perversion of sensation similar to that occurring from the lesions of the thalamus may be produced by this disturbance.[3, 4] There is no disturbance in the other modalities of sensation which pass in the mesial fillet.

Cerebellar Signs. Dizziness, vertigo, falling to either side and disturbances of equilibrium are caused by the involvement of the restiform body, the spinocerebellar tracts and Deiters' nucleus. Nystagmus is attributed to the irritation of Deiters' nucleus and the ocular connections through the posterior longitudinal bundle.[3, 5, 6, 9] It is suggested that in those cases without nystagmus but with cerebellar signs, only the posterior part of the cerebellum is affected or only the spinocerebellar tracts are interrupted. Furthermore, in those patients having nystagmus without cerebellar signs, it would appear possible that the lesion involves only the ocular connections to the posterior longitudinal bundle.

Although weakness of the lateral rectus muscle was not observed, diplopia could conceivably be explained on this basis because the abducens nucleus is sometimes supplied by the PICA. Also, softening may extend to include the VI nerve nucleus.[6] On the other hand, interruption of the ocular connections from Deiters' nucleus also could be responsible for diplopia.

Sympathetic Disturbances. The softening intercepts the reticular formation containing the ipsilateral sympathetic pathway, producing sympathetic paralysis. This is known as Horner's syndrome and consists of ptosis of the upper eyelid, miosis, enophthalmos, anhidrosis and flushing of the same side of the face and smoothing of the ipsilateral facial muscles. Loss of sympathetic stimulation to the nonstriated part of the levator palpebrae superioris produces the ptosis. However, this is a pseudoptosis, as the patient is able to raise the lid, the voluntary portion of the muscle being supplied by the III nerve, which is unaffected. The paralysis of the dilator pupillae causes miosis. The pupil does not dilate, but it will contract in response to light. Enophthalmos is caused by the elevation of the lower lid, although some ascribe it to paralysis of the muscle of Müller.[9] Vasomotor and secretory changes are inconstant features.

Weakness of the facial muscles on the ipsilateral side may be due to lack of tone secondary to the sympathetic disturbances. In all 19 patients in whom facial paresis was observed there was a definite Horner's syndrome. Moreover, in none of the three patients without evidence of sympathetic disturbance was weakness of the facial muscles noted. However, the facial nucleus extends into the medulla,[9] so that softening could include this nucleus and produce facial paresis [5] or actual paralysis.[6]

Cranial Nerves of the Medulla. Vomiting is caused by irritation of the vomiting center near the dorsal nucleus of the vagus lying under the floor of the fourth ventricle. Involvement of the nucleus ambiguus produces ipsilateral paralysis of the vocal cord, causing hoarseness. Affection of this nucleus also causes paralysis of the muscles of the pharynx and soft palate, contributing to the dysphagia and aggravating the dysphonia. The gag reflex on the ipsilateral side is absent, because the sensory nuclei of the IX and X nerves are affected.

Hiccough is said to be due to involvement of the respiratory center located in the reticular formation.[7]

A dry, annoying cough was observed in some cases, apparently a consequence of the dysphagia and aspiration of secretions, water or food into the respiratory passages.

Pyramidal Tract Involvement. The paresis of the extremities and the signs of involvement of the pyramidal tract are thought due to the edema which appears around the thrombosed area.[4] However, this would not explain the persistence for from six months to two years of hemiparesis in three otherwise typical cases. Occlusion of the vertebral artery must be considered in these cases because it produces a similar picture when such paresis is persistent. The differential diagnosis between thrombosis of the vertebral artery and the PICA is almost impossible under such circumstances.[10, 11]

Later Clinical Course

We have been able to determine the late outcome in 20 of the 28 cases. Ten patients died. Of these, seven died at the first hospital admission, the time of death varying from 12 hours to eight months after entry. There was no autopsy in these cases. The clinical diagnoses of the causes of these deaths were: hypertensive heart disease with congestive failure (one case); bronchopneumonia (two cases); recurrent stroke (two cases); and, in two cases, death was considered due to the PICA thrombosis itself or to an undiagnosed fulminant complication within 48 hours of the onset of the original lesion.

Three of the patients died from one to eight years after leaving the hospital, in each case the cause of death appearing to be apoplexy. Thus five, or 50 per cent of subsequent deaths, were due to recurrent acute cerebral vascular lesions.

There were 11 patients living at the time of this report, all in good general health. We have reëxamined 10 of these patients from six months to 12 years after their episodes. There were certain persistent complaints and neurologic abnormalities, as mentioned in the discussion of the individual symptoms and findings. Eight of the 10 survivors had successfully returned to their previous occupations, although one patient continued to have episodes of vertigo or dizziness, sometimes with falling. The same complaints greatly restricted the activity of the other two survivors.

Summary

The findings in 28 cases of thrombosis of the posterior inferior cerebellar artery are presented, with an analysis of the symptoms and neurologic abnormalities.

In most cases there was a sudden onset of vertigo, falling, unilateral ataxia, vomiting, diplopia, paresthesias, dysphagia and dysphonia.

Horner's syndrome, cerebellar signs, unilateral palatal paralysis, ipsilateral loss of pain and temperature perception of the face and contralateral loss on the trunk and extremities were observed.

Late follow-up examinations in 10 cases revealed a persistence of certain abnormalities.

Although most cases presented all or most of the typical signs and symptoms, it is emphasized that there was much variation in the clinical picture, due to differences in their relative severity.

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DETECTION OF HEART DISEASE IN A MASS CHEST X-RAY SURVEY FOR TUBERCULOSIS CASE-FINDING *

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The value of early diagnosis of heart disease is well recognized. When cardiac conditions are detected in the earliest possible stages, the course of the disease may be arrested or retarded and the patient permitted to live a useful life within the limits of his capacity. Unfortunately, our present diagnostic aids are not sufficiently sensitive to reveal all latent abnormalities which may later lead to acute or chronic heart disease. Therefore, negative findings from cardiac examination cannot be considered a guarantee of absence of heart disease. However, positive findings are of great value in revealing the need for a therapeutic regimen.

The use of screening technics developed in other areas of public health work has been advocated for the control of cardiovascular diseases.[1, 2, 3] To determine the utility of a given screening technic for the detection of cases of some specific disease, three questions must be posed: Can the test be performed at relatively low cost per person tested? Is relatively little time required of the participating physicians? Is the test productive of a fair number of previously unknown cases?

One promising method of detecting heart disease is mass surveys with roentgenograms of the chest. A study of the usefulness of a survey which was designed primarily for the detection of tuberculosis for revealing cardiovascular disease was recently conducted by the Queensboro Tuberculosis and Health Association. A typical survey, in which roentgenograms of the chest of 6,579 persons over 15 years of age were made in mobile units using 70 mm. film, was selected for the study. These plates were read by a team of specialists who had had considerable experience with miniature films. Abnormality of the heart was suggested by 87 of the roentgenograms. These persons were invited to the Association's headquarters for examination "for a condition other than tuberculosis."

The examination consisted of a complete history taken by a nurse in conformity with standards of the American Heart Association, a 14 inch by 17 inch chest roentgenogram taken at a distance of 6 feet, a 9-lead electrocardiogram, measurement of the blood pressure and physical examination.

Of the 87 persons, 19 were found to have heart disease which was previously unknown, 26 had cardiovascular disease which was previously known, and 25 were found to be free of organic heart disease. Of these 25, nine were found to have essential hypertension on the basis of blood pressure readings exceeding 150/100 mm. of Hg. The remaining 17 persons did

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not reply to the invitation for examination. In this series, then, about one out of every four persons who returned for reëxamination was found to have previously unknown organic cardiovascular disease.

These findings compare favorably with the productivity of the survey from the point of view of tuberculosis case-finding. A total of 126 persons was recalled because of suspected pulmonary disease. Of these, nine were found to have active tuberculosis and 72 were diagnosed as arrested, apparently cured or questionable tuberculosis (table 1).

TABLE 1

Incidence of Heart Disease and Pulmonary Tuberculosis Uncovered by the Woodside Chest X-Ray Survey, November, 1950

			Number	
Heart Disease				
Total x-rayed			6,579	
Recalled for follow-up because of cardiovascular abnormality on 70 mm. x-ray			87	
Responded to follow-up request, thus facilitating final diagnosis			70	
Attended cardiac follow-up session at Association	56			
Follow-up by private physician	14			
No response to follow-up request; final diagnosis unavailable			17	
Final Diagnoses of 70 Persons Who Responded to Follow-up Request				
No evidence of organic cardiovascular disease (essential hypertension noted in 9 of these patients)			25	
Organic heart disease			45	(.7%)
Hypertensive arteriosclerotic heart disease	32			
Rheumatic heart disease	12			
Arteriosclerosis without hypertension	1			
Patients whose cardiac disease was unknown to them		19	(.3%)	
Patients with known cardiac history		26		
Not under treatment at present	8			
Under treatment at present	18			
Respiratory Tuberculosis				
Total x-rayed			6,579	
Recalled for pulmonary abnormalities			126	
TBC discovered			81	
Active—minimal	4			
moderately advanced	5	.14%		
Arrested	46			
Apparently cured	19			
Activity undetermined	6			
Questionable lesion	1			

Of the cases of heart disease, both known and unknown, 32 had hypertensive and arteriosclerotic heart disease, 12 had rheumatic heart disease and one had arteriosclerotic heart disease without hypertension.

Reports of the examinations were sent to the subjects' private physicians when findings were negative as well as when they were clinically significant. Two persons who did not have physicians agreed to have their reports sent to hospital clinics.

Most of the cases of rheumatic disease were previously known, whereas more than half the cases of hypertensive arteriosclerosis were discovered for the first time through the chest roentgen-ray survey.

Table 2 shows the distribution of findings according to age, race and sex. Previously unknown cases of hypertensive arteriosclerosis were found in every age group over 24 years. However, since the sample of persons examined by roentgen-ray followed, roughly, the population curve, findings of arteriosclerosis among people over 55 years of age were proportionately higher than among younger people.

An indication of the proportion of 70 mm. thoracic roentgenograms which may be expected to suggest cardiac abnormalities is given in table 3. Of the 30,072 persons who had chest films taken in the Queensboro Tu-

TABLE II

Cardiac Abnormalities (New and Known Cases) According to Age, Race and Sex

Age	Total All Findings	Hypertensive Arteriosclerosis			Rheumatic Heart Disease			Arteriosclerosis Without Hypertension		
		M	F	Total	M	F	Total	M	F	Total
15–24	1					1	1			
25–34	2	1		1		1	1			
35–44	10	2*	1	3		6	6	1		1
45–54	9	2	4	6	1	2	3			
55–64	8	2	5	7		1	1			
65–74	13	7	6	13						
75 and over	2	1	1	2						
Total	45	15	17	32	1	11	12	1		1

Cardiac Abnormalities (New Cases) According to Age, Race and Sex

Age	Total All Findings	Hypertensive Arteriosclerosis			Rheumatic Heart Disease		
		M	F	Total	M	F	Total
15–24	1					1	1
25–34	1	1		1			
35–44	2	2*		2			
45–54	5	1	3	4		1	1
55–64	3	1	2	3			
65–74	6	3	3	6			
75 and over	1	1		1			
Total	19	9	8	17		2	2

* One colored.

berculosis and Health Association's $1 X-ray Service during 1949 and 1950, slightly more than 1 per cent were recalled for pulmonary follow-up and approximately 2.5 per cent had abnormal cardiac shadows. Both these percentages may be a little higher than would be found in a random sample of the population because a large number of persons attending the $1 X-ray Service were referred by physicians who suspected the existence of thoracic disease.

In the opinion of this writer, the proportion of films of the chest which will be considered to indicate cardiac examination in future studies may be decreased as clinicians develop greater skill in interpretation. Not un-

TABLE III

Dollar X-Ray Service
(Screening Film)

Year	Total X-Rays	Indicative of Tuberculosis	Indicative of Cardiac Disease
1949	15,820	203	426
1950	14,252	154	378
Total	30,072	357	804

commonly, a 4-foot 70 mm. film of the chest will indicate enlargement of the heart when a 6-foot 14 inch by 17 inch film will show that the size of the heart is within normal limits. In this writer's experience with 70 mm. chest films, abnormalities in the contour of the cardiac shadows proved to be more significant than apparent enlargement of the heart.

CONCLUSIONS

Mass surveys using thoracic roentgenograms for the detection of previously unknown, clinically significant cardiovascular disease meet the qualifications for an efficient screening process. Application of the technic to revealing heart disease compares favorably with its use in the detection of tuberculosis in productivity, in time required by participating physicians and in administrative cost. The method has recognized limitations, but some of these may disappear as refinements are introduced.

ACKNOWLEDGMENT

The author is indebted to Miss Fowler, of the staff of the Queensboro Tuberculosis and Health Association, for editorial help, and to J. Beeber & Co., Inc., for furnishing the Beck Lee Electrocardiograph for use in the survey.

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PHYSIOLOGIC FACTORS IN THE TREATMENT OF CHRONIC HYPERTROPHIC PULMONARY EMPHYSEMA *

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The difficulties involved in the treatment of chronic pulmonary emphysema have recently been emphasized, especially the undesirable reactions that may follow the administration of oxygen in markedly anoxic patients. Comroe [1] observed the development of mental changes ranging from somnolence to coma in eight of 65 patients with mild to severe chronic anoxemia, who were given high concentrations of oxygen to breathe. Godfrey, Pond and Wood studied an emphysematous patient who became comatose within five minutes after treatment with 90 to 97 per cent oxygen, and regained consciousness with equal rapidity when oxygen was discontinued.[2] Davies and Mackinnon mentioned two patients with cor pulmonale who showed neurologic changes during oxygen administration, one of whom became comatose within two hours and died after four hours of oxygen treatment.[3] Donald mentions a patient who went into coma after 12 hours of oxygen therapy but regained consciousness shortly after oxygen was withdrawn.[4]

In cases of congestive failure, pulmonary emphysema and fibrosis treated with moderate concentrations of oxygen, i.e., 40 to 50 per cent oxygen, Barach and Richards [5, 6, 7, 8] reported no adverse mental changes in the patients studied but did mention an increased tendency to sleep associated with progressive relief of orthopnea and dyspnea. The development of irrationality, depression and stupor was subsequently described by Barach [9] as an occasional consequence of oxygen treatment; a comatose state took place in one patient with pulmonary emphysema which persisted for five days, terminating spontaneously into a rational cheerful disposition as long as the oxygen supply was not interrupted. Since 1938 Barach has emphasized that these untoward symptoms were prevented by a regulated program of oxygen treatment in which the oxygen concentration breathed by the patient was begun at a low concentration and increased very gradually.[10, 11] In addition, a similar type of irrationality which took place in patients with cerebral arteriosclerosis, as a result of breathing high concentrations of oxygen, was likewise prevented by a similar program of graduated increase in the percentage of oxygen in the inspired air.[12] Goggio [13] and Baldwin, Cournand and Richards [14] emphasized the value of oxygen therapy when

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† With the technical assistance of Doris Gates, A.B.

properly administered for the relief of acute anoxic states in patients with pulmonary emphysema, but they cautioned against the use of continuous prolonged therapy in chronically anoxic patients in whom termination of treatment provoked recurrence of dyspnea.

The intention of this paper is to present additional studies that bear on the physiologic and clinical factors involved in oxygen treatment in pulmonary emphysema and, in addition, recent observations on the relief of bronchial spasm and the overinflation of the lungs that characterize this clinical entity.

Methods of Investigation

(A) *Effect of Inhalation of Oxygen:* The resting pulmonary ventilations were recorded spirographically in 10 normal subjects who exhibited no evidence of pulmonary disease, while breathing room air for 15 minutes, followed by a 15 minute period of 100 per cent oxygen. These studies were repeated in 25 patients with mild to severe pulmonary emphysema with no evidence of cardiac insufficiency.

A closed circuit Benedict-Roth ventilometer was employed, with a motor blower on the inspiratory side to overcome the slight resistance of the one-inch tubing and the soda lime. Close to the mouthpiece, two high-velocity valves served to prevent the accumulation of expired carbon dioxide. Straight line graphs of pulmonary ventilation were obtained by replacing continuously the oxygen consumed by the subject and removed from the bell.

Studies of ventilatory function included vital capacity and maximal breathing capacity. A tracing of four consecutive determinations of vital capacity revealed the air trapped in the lungs, by measuring the difference between the maximal expiratory position of the first and last vital capacity. This reading is expressed as cubic centimeters of gas trapped in the lung and is a reflection of the amount of gas which the subject fails to expire on subsequent deep breaths.

(B) *Effect of Bronchodilator Drugs:* Studies of ventilatory function were performed on a group of patients with pulmonary emphysema, some of whom had clinical evidence of bronchospasm. Tracings were taken before and 20 minutes after the inhalation of 0.3 c.c. of a 2.25 per cent racemic epinephrine aerosol.*

Similar studies were performed following the ingestion of 0.3 gm. aminophylline with tracings taken 30 minutes and 60 minutes after administration. Control studies in the same group were made by substituting placebos for oral aminophylline and repeating the above studies.

(C) *Changes in Acid-base Balance:* Four patients with moderately advanced pulmonary emphysema were given 100 per cent oxygen by the Meter mask for periods of three hours. Samples of arterial blood from the

* The Vaponefrin nebulizer and solution were used in these studies.

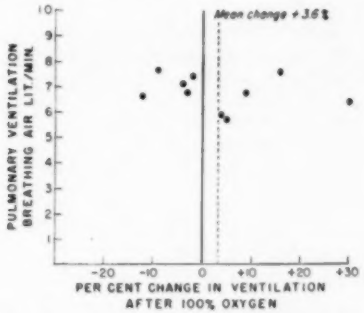

FIG. 1. Graphic illustration of the per cent change in pulmonary ventilation while breathing 100 per cent oxygen as compared to air in 10 normal individuals.

femoral artery were drawn before and at the conclusion of the experimental period. The specimens were analyzed for carbon dioxide content, serum chlorides and pH of arterial blood.

RESULTS

The normal subjects showed no significant change in the resting pulmonary ventilation on breathing 100 per cent oxygen (figure 1). Twenty-one of the 25 patients with pulmonary emphysema exhibited a significant fall in resting pulmonary ventilation while breathing 100 per cent oxygen, comparable to previously reported findings. In only one patient was there

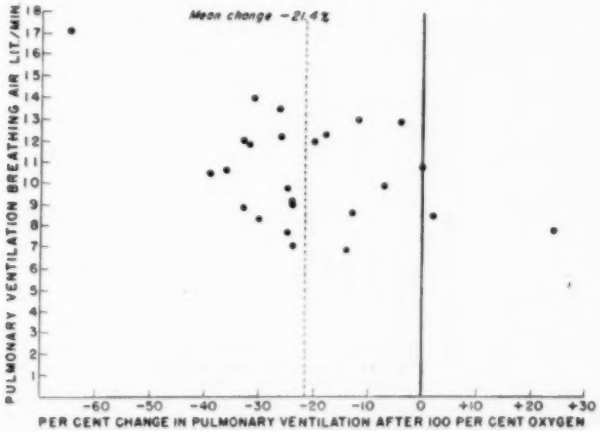

FIG. 2. Comparison of pulmonary ventilation and maximal breathing capacity in 100 per cent oxygen in 25 patients with pulmonary emphysema expressed as per cent change from air breathing.

TABLE I

Effect of Breathing 100 Per Cent Oxygen in Patients with Pulmonary Emphysema

Case No.	Pulmonary Ventilation			Maximum Breathing Capacity		
	Liters per Minute			Liters per Minute		
	Air	100% O_2	% Change	Air	100% O_2	% Change
1	17.1	5.9	−65			
2	10.6	6.9	−36			
3	7.1	5.4	−24			
4	9.1	6.9	−24			
5	6.9	5.9	−14			
6	12.0	9.6	−20			
7	12.3	10.1	−18			
8	12.1	8.1	−33	46.7	41.0	−12
9	12.3	9.1	−26	17.7	19.9	+16
10	7.8	9.7	+24	23.7	29.6	+25
11	10.8	10.8	0	94.0	103.2	+10
12	8.7	7.6	−13	13.6	13.6	0
13	10.5	6.4	−39			
14	8.9	6.8	−24			
15	13.0	11.4	−12	47.2	47.2	0
16	11.9	8.1	−32			
17	8.5	8.7	+ 2			
18	14.0	9.7	−31	29.6	38.4	+30
19	7.7	5.8	−25	29.6	32.3	+ 9
20	13.5	10.0	−26	59.4	60.9	+ 2
21	8.1	5.7	−30	30.2	33.4	+10
22	8.8	5.9	−33	56.0	71.1	+27
23	12.9	12.4	− 4	24.2	29.6	+22
24	9.7	7.3	−25	12.9	14.5	+12
25	9.9	9.2	− 7	32.3	37.9	+19
Mean			−21.4			+12

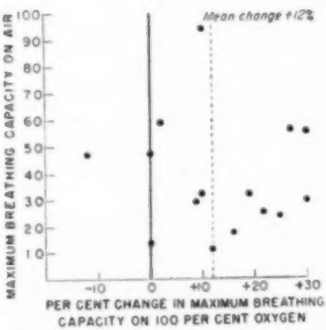

FIG. 3. Comparison of pulmonary ventilation and maximal breathing capacity in 100 per cent oxygen in 25 patients with pulmonary emphysema expressed as per cent change from air breathing.

an appreciable rise. The mean decrease for the group as a whole was 21.4 per cent, expressed as per cent of change from the control level (figure 2). The vital capacities of 14 patients in this series were determined for air and 100 per cent oxygen and showed no appreciable change. However, 11 of the 14 exhibited an increase in the maximal breathing capacity when breathing 100 per cent oxygen, the mean rise being 12 per cent (table 1, figure 3).

The inhalation of 0.3 c.c. of a 2.25 per cent racemic epinephrine aerosol in the patient group resulted in an increase in vital capacity, the mean change being 18.3 per cent (table 2, figure 4). In addition, the degree of "trapping" was considerably reduced (figure 5). An appreciable number of patients in this group exhibited no evidence of bronchospasm clinically at the time the spirographic tracings were made. The maximal breathing capacities

TABLE II

Effect of 2.25 Per Cent Racemic Epinephrin Aerosol on Vital Capacity and Maximal Breathing Capacity in Patients with Pulmonary Emphysema

Case No.	Vital Capacity			Maximal Breathing Capacity		
	Liters per Minute			Liters per Minute		
	Before	After	% Change	Before	After	% Change
1	1.8	1.8	0	90.5	88.5	− 2.5
2	0.6	1.4	+133.2	26.5	40.0	+ 51.0
3	2.5	2.5	0	40.6	48.8	+ 20.2
4	0.8	0.8	0	14.5	14.5	0
5	3.4	3.4	0	41 0	62.0	+ 51.3
6	2.3	3.2	+ 39.0	19.9	23.6	+ 18.4
7	3.6	3.6	0	103.2	125.4	+ 21.3
8	2.1	2.2	+ 4.8	13.6	15.2	+ 11.8
9	2.5	3.0	+ 20.8	47.2	54.0	+ 14.7
10	3.4	3.0	− 12.8	71.1	64.6	− 9.2
11	4.2	4.5	+ 8.6	51.2	51.2	0
12	2.6	3.2	+ 25.6	26.4	41.0	+ 55.3
13	2.4	3.8	+ 56.5	23.9	59.1	+147.8
14	2.3	2.6	+ 13.2	33.2	41.3	+ 24.2
15	2.4	2.5	+ 2.2	38.3	33.8	− 11.8
16	1.5	1.5	0	17.6	20.7	+ 17.6
17	2.5	3.2	+ 28.0	24.4	38.0	+ 55.7
18	3.8	3.8	0	38.6	42.6	+ 10.3
19	1.4	2.6	+ 85.6	22.1	41.3	+ 86.8
20	2.3	2.6	+ 13.0	17.7	20.7	+ 16.9
21	1.8	2.3	+ 27.8	32.5	38.4	+ 18.1
22	2.8	2.8	0	42.3	45.0	+ 6.1
23	3.3	3.4	+ 3.0	32.3	40.4	+ 25.0
24	4.8	4.8	0	82.2	117.8	+ 43.0
25	2.0	2.3	+ 15.0	23.7	50.0	+110.9
26	2.7	2.8	+ 3.6	26.7	42.6	+ 59.5
27	2.4	2.8	+ 16.6			
28	2.8	3.3	+ 17.9			
29	1.3	1.7	+ 30.8			
30	2.6	3.1	+ 19.2	29.6	32.3	+ 9.0
Mean			+ 18.3			+ 32.0

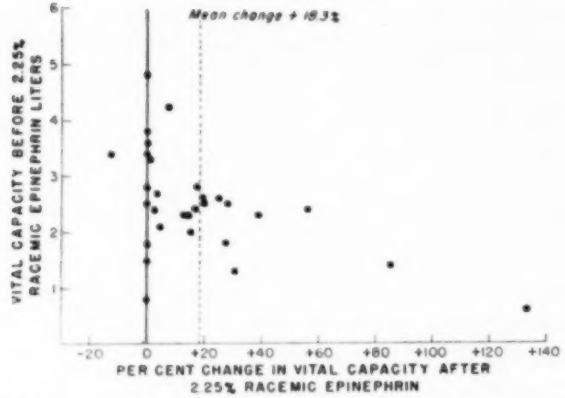

FIG. 4. Studies on vital capacity and maximal breathing capacity in 29 patients with pulmonary emphysema following the inhalation of 0.3 c.c. of 2.25 per cent racemic epinephrine expressed as per cent change.

(figure 6) and breathing reserves were significantly increased, with a mean change of 32 per cent and 8.4 per cent, respectively.

When similar studies were performed following the ingestion of 0.3 gm. aminophylline (table 3), the mean rise in vital capacity at the end of 30 minutes was 7.3 per cent. At the end of 60 minutes, however, the mean rise was 12.9 per cent. The maximal breathing capacity was significantly elevated for both periods: 23.4 per cent at 30 minutes and 45.8 per cent at the end of an hour (figures 7 and 8).

These results are in striking contrast to the data obtained when a placebo similar in appearance was substituted for aminophylline. The vital capacity

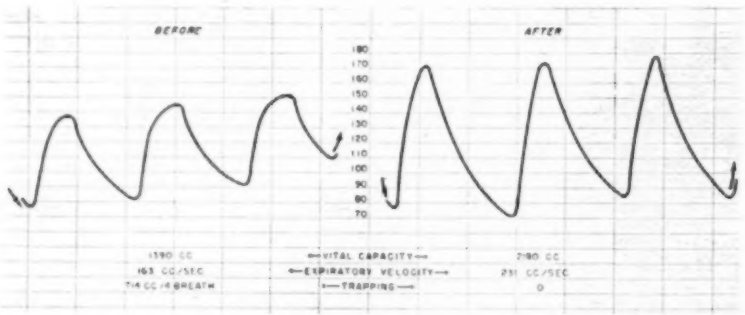

FIG. 5. Spirographic tracing illustrating the effect of bronchodilator aerosol on expiratory velocity and "trapping" in a patient with pulmonary emphysema.

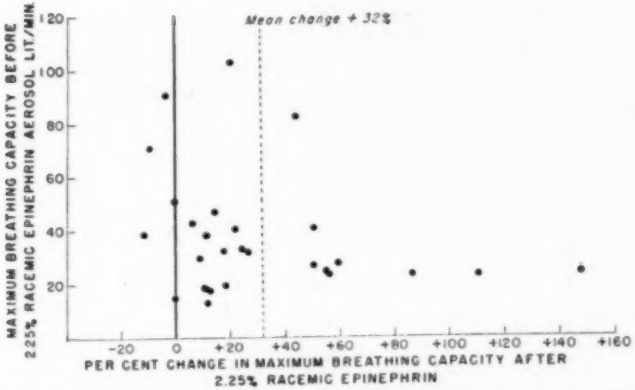

FIG. 6. Studies on vital capacity and maximal breathing capacity in 29 patients with pulmonary emphysema following the inhalation of 0.3 c.c. of 2.25 per cent racemic epinephrine expressed as per cent change.

TABLE III

Effect of 0.3 Gm. Oral Aminophylline on Vital Capacity and Maximal Breathing Capacity in Patients with Pulmonary Emphysema

Case No.	Vital Capacity					Maximal Breathing Capacity				
	Liters/Minute			% Change		Liters/Minute			% Change	
	Before Aminophyl.	½ Hour After	1 Hour After	½ Hour After	1 Hour After	Before Aminophyl.	½ Hour After	1 Hour After	½ Hour After	1 Hour After
1	3.0		3.2		+ 7.4	67.5		70.3		+ 4.2
2	2.6		3.4		+33.0	11.9		20.1		+ 69.0
3	2.1	2.8		+32.1		28.9	44.9		+55.6	
4	3.3		3.5		+ 7.6	31.4		43.7		+ 39.0
5	3.2		3.5		+ 8.8	20.5		53.9		+163.0
6	3.0		3.5		+15.1	56.8		73.1		+ 28.7
7	1.3	1.7		+29.0		29.2	42.8		+46.5	
8	1.9	2.0		+ 4.6		19.5	26.3		+34.7	
9	3.3	4.1		+23.3		36.3	49.8		+37.1	
10	1.7		2.0		+19.8	27.5		31.2		+ 13.5
11	3.2	4.0		+26.6		42.8	50.6		+18.2	
12	2.6	3.0		+13.8		35.4	54.8		+55.0	
13	2.3	2.4		+ 6.7		57.0	55.0		- 3.5	
14	3.8	3.8		0		38.6	42.6		+10.4	
15	1.0	0.9		-16.5		10.9	10.9		0	
16	1.2		1.5		+25.9	9.9		17.8		+ 80.2
17	5.2	4.8		- 7.7		61.8	55.8		- 9.8	
18	3.6	3.9		+ 7.5		95.5	109.0		+11.8	
19	4.7	4.8		+ 3.5		58.8	79.1		+34.5	
20	2.3		2.6		+15.6	17.7		20.7		+ 17.0
21	2.7		3.2		+17.4	23.7		32.4		+ 37.0
22	1.8	1.7	1.5	- 6.2	-20.5	20.7	17.7	17.7	-14.4	- 14.4
23	2.0	1.8	2.2	- 9.5	+ 7.0	9.8	13.8	19.7	+40.3	+100.5
24	1.9	1.8	2.2	- 6.0	+15.6	23.8	25.1	35.4	+ 5.7	+ 48.8
25	2.3	2.4	2.4	+ 4.8	+ 2.8	34.0	35.2	38.1	+ 3.5	+ 11.9
26	1.9	2.3	2.4	+17.8	+25.7	20.6	35.3	29.4	+71.4	+ 42.7
Mean				+ 7.3	+12.9				+23.4	+ 45.8

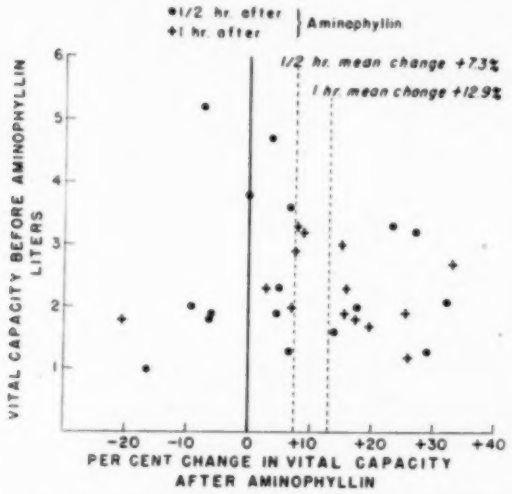

FIG. 7. Change in vital capacity and maximal breathing capacity following ingestion of 0.3 gm. of aminophylline in per cent of the control level.

was not significantly altered in either the 30 or 60 minute periods (figure 9). Maximal breathing capacity was increased slightly at the 30 minute period, with a mean rise of 5.8 per cent, but fell at the end of 60 minutes to 3.9 per cent below the control level (table 4, figure 10). These variations were not significant.

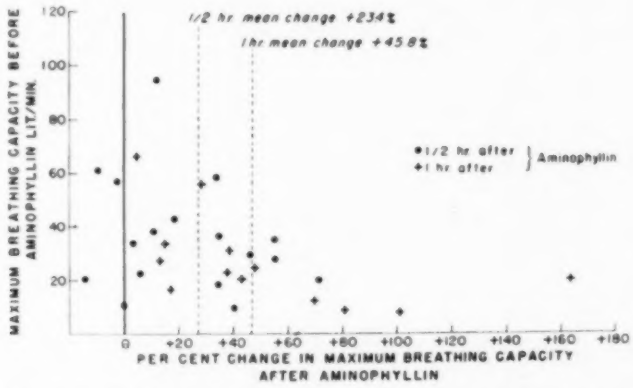

FIG. 8. Change in vital capacity and maximal breathing capacity following ingestion of 0.3 gm. of aminophylline in per cent of the control level.

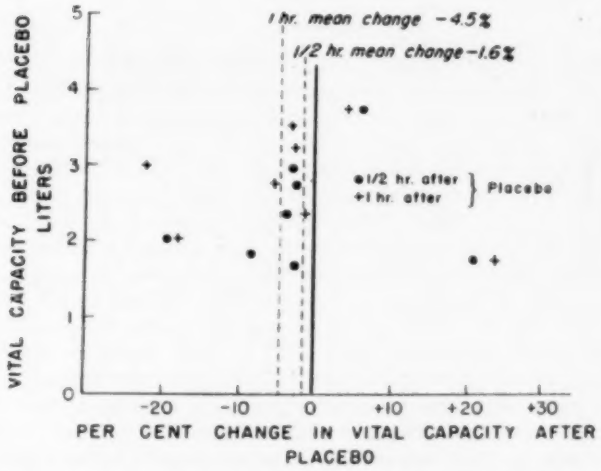
1 hr. mean change −4.5%
1/2 hr. mean change −1.6%
●1/2 hr. after
+1 hr. after
Placebo
VITAL CAPACITY BEFORE PLACEBO LITERS
PER CENT CHANGE IN VITAL CAPACITY AFTER PLACEBO

FIG. 9. Change in vital capacity and maximal breathing capacity following ingestion of a placebo in per cent of the control level.

Blood and electrolyte studies on four patients before and after inhaling 100 per cent oxygen for three hours revealed striking evidence of respiratory acidosis, with a fall in blood pH, rise in the carbon dioxide content and fall in the serum chlorides (figure 11). Two of the patients became drowsy and all exhibited some agitation. Coma or disorientation was not encountered.

TABLE IV

Effect of Placebo Tablet on Vital Capacity and Maximal Breathing Capacity in Patients with Emphysema

Case No.	Vital Capacity			Maximal Breathing Capacity		
	Before Placebo (Liters per Minute)	Half Hour After (% Change)	One Hour After (% Change)	Before Placebo (Liters per Minute)	Half Hour After (% Change)	One Hour After (% Change)
1	1.8	− 8.5		32.5	+14.9	
2	3.2		− 2.6	73.5		−15.9
3	1.7	− 2.7		35.3	+17.3	
4	3.6		− 3.1	47.1		+10.4
5	1.8	+20.8	+23.9	27.3	+13.9	+29.5
6	3.0	− 3.0	−22.4	46.8	−50.0	−50.0
7	2.7	− 2.2	− 5.5	40.8	+57.2	−21.3
8	2.4	− 3.8	− 1.3	33.3	− 5.9	− 7.8
9	2.0	−19.8	−18.0	11.8	− 0.4	+16.3
10	3.8	+ 6.4	+ 4.0	25.5	− 0.4	+ 7.5
Mean		− 1.6	− 4.5		+ 5.8	− 3.9

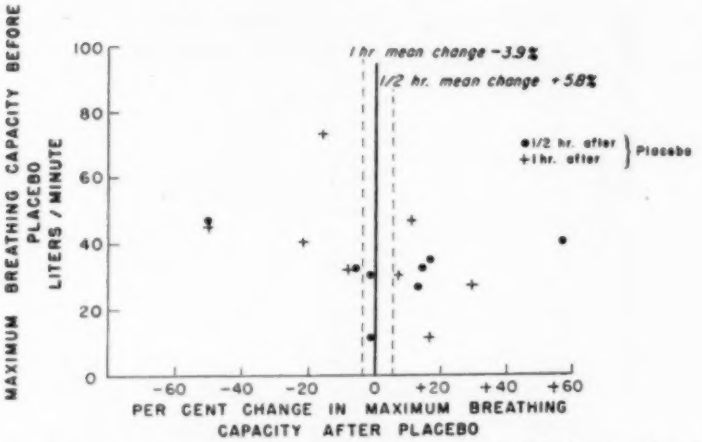

FIG. 10. Change in vital capacity and maximal breathing capacity following ingestion of a placebo in per cent of the control level.

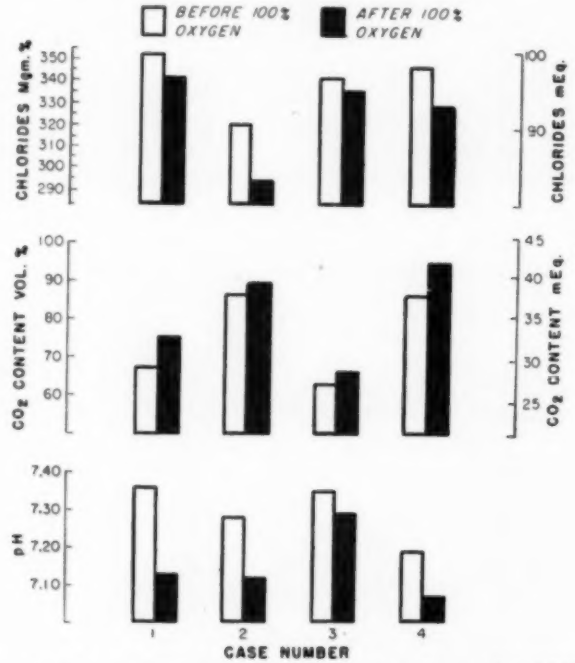

FIG. 11. One hundred per cent oxygen was inhaled for three hours. Arterial blood studies in four patients reveal the presence of respiratory acidosis.

Discussion

Dripps and Comroe [15] and Otis et al.[16] studied the effect on respiration when 100 per cent oxygen was inhaled by normal individuals. They noted a slight depression in the pulmonary ventilation during the first two minutes, followed by a mild stimulation after eight minutes averaging 7.6 per cent. It was postulated that the latter effect might be due either to the local irritant nature of 100 per cent oxygen on the respiratory tract or to pulmonary capillary dilatation, producing reflex respiratory stimulation as a result of slight pulmonary congestion (von Euler and Liljestrand [17]).

A reduction in pulmonary ventilation on inhaling oxygen was first observed in 1908 by Beddard and Pembrey [18] in a patient with pulmonary congestion due to heart failure, and, later, by Campbell and Poulton [19] in patients with chronic pulmonary disease. The latter investigators observed a corresponding increase in the carbon dioxide concentration in the expired air. In 1921, Barach and Woodwell [20] reported an elevation of the arterial oxygen saturation in patients with cardiac insufficiency on inhaling 40 to 50 per cent oxygen, with an increase in the arterial carbon dioxide content. In two patients with lethargic encephalitis, the carbon dioxide content rose from 60 to 88 vol. per cent in one and one-half hours.

In the studies of Barach and Richards' patients with advanced pulmonary disease and cardiac failure, a consistent elevation in the arterial carbon dioxide tension was related to the decrease in pulmonary ventilation resulting from the inhalation of the oxygen-enriched atmosphere.[6, 7] This increase in arterial carbon dioxide was also recognized as a homeostatic mechanism which allowed a greater elimination of carbon dioxide per breath. In these cases, no significant change in pH was reported, even in the presence of gradually increasing arterial carbon dioxide content. The patients were observed in respect to the physiologic and clinical effects of long-term inhalation of 40 to 50 per cent oxygen in an oxygen chamber or tent. In some cases a gradual fall in the arterial carbon dioxide content toward the normal level took place despite continuance of oxygen treatment. The decrease in arterial carbon dioxide during oxygen therapy indicated a favorable prognosis with respect to clinical improvement as a result of oxygen therapy. In some cases, the inhalation of 100 per cent oxygen did not always show an immediate fall in pulmonary ventilation in patients with emphysema, since this response may be obscured by the factor of respiratory obstruction due to bronchospasm and congestion of the bronchial mucosa.[10]

The mental changes have been ascribed to a number of possible mechanisms, including carbon dioxide narcosis, cerebral vasospasm, depression of the cerebral cortex and respiratory acidosis. Baldwin, Cournand and Richards [14] have emphasized the factor of carbon dioxide retention following hypoventilation induced by oxygen therapy. Barach,[21] on the other hand, has stressed the factor of respiratory acidosis as the cause of the comatose state, since elevation of carbon dioxide without acidosis (i.e., acid shift in pH) did not result in coma in cases treated over long periods of time. He

previously emphasized the importance of a gradual increase of the oxygen concentration inhaled by the patient, to avoid the occurrence of an irrational or comatose state.[10, 11] Irrationality took place after two hours' inhalation of 100 per cent oxygen in a patient with pulmonary emphysema, with a carbon dioxide content of 70 vol. per cent and a pH of 7.2, whereas no mental changes were observed in a patient whose arterial carbon dioxide rose to 120 vol. per cent with a normal pH, after the oxygen concentration of the inspired air had been gradually increased.

Comroe [1] mentions the occurrence of drowsiness in four patients whose PCO_2 was between 52 and 77 mm. of mercury (70.3 and 104.4 vol. per cent) during inhalation of oxygen. In two patients with bronchial asthma and functional pulmonary emphysema, with severe anoxia, a comatose state developed during the administration of 50 to 70 per cent oxygen.[21] The inhalation of high concentrations of oxygen was accompanied by retention of carbon dioxide and a fall in pH. In one case, a child, marked improvement was noted following intravenous infusion of 200 c.c. of N/6 sodium lactate. The serum pH rose from 7.08 to 7.27 on completion of infusion.

Three of the four patients in our series exhibited mental changes accompanied by a severe respiratory acidosis. Restitution to normal took place within a short time on cessation of oxygen administration.

Partial bronchial obstruction, resulting either from spasm of the bronchial musculature or from an excessive production of mucus, is a frequent occurrence in pulmonary emphysema. Many observers [10, 22, 23, 24, 25] have noted the improvement in such patients upon administration of bronchodilator and vasoconstrictor aerosols. Baldwin, Cournand and Richards [14] have shown that the mildly emphysematous patient usually performs the maximal breathing capacity in a state of hyperinflation as revealed by spirographic tracings. More rapid ventilation was performed at a lower state of inflation following the use of a bronchodilator spray. They found that the daily use of such aerosols over long periods resulted in considerable benefit and that there was no evidence of harm.

Our observations of the effect of inhaling 0.3 c.c. of a 2.25 per cent racemic epinephrine aerosol in patients with pulmonary emphysema are in accord with the views expressed above. The graphic demonstration of a reduction in pulmonary hyperinflation, expressed as "trapping," is evident. Barach and Garthwaite [26] have outlined the value and limitations of bronchodilator aerosols for the treatment of protracted bronchospasm, especially the treatment of the refractory state which ultimately develops in many patients with bronchial asthma and the bronchospastic type of pulmonary emphysema.

Considerable literature has accumulated during the past 10 years on the use of aminophylline in the treatment of asthma. With few exceptions, these papers emphasize the beneficial effect of intravenous administration. At the present time, there is still considerable doubt as to the effectiveness of orally administered aminophylline in the treatment of pulmonary disease

associated with bronchospasm. Bernhardt [27] in 1941, reporting on five cases of asthma, remarked that aminophylline was ineffective when given orally. Barach [12] found that the administration of aminophylline by mouth on an empty stomach was a valuable method of producing relaxation of the bronchi in a considerable proportion of patients with pulmonary emphysema.

Objective evidence of the value of oral aminophylline is apparent from the spirographic tracings obtained in our series. Patients were tested in a basal state. The rise in both vital capacity and maximal breathing capacity at the end of one hour as compared to the data following a placebo offers experimental support concerning the effectiveness of oral aminophylline when employed for the relief of bronchospasm.

Remarks on Clinical Management

Sufficient evidence has been presented regarding the effectiveness of the bronchodilator aerosols, aminophylline and ephedrine in the treatment of pulmonary emphysema. With constant use, the likelihood that a state of refractoriness to these agents will develop, is enhanced. Clinical experience indicates that these patients do well at first and then gradually become refractory. In many respects, the management of the patient with pulmonary emphysema with bronchospasm is similar to that of the patient with bronchial asthma, namely, treatment of the refractory state. To restore sensitivity to the bronchodilator drugs, the following program has been employed:

1. Complete bed rest with avoidance of physical exertion is insisted upon.
2. Demerol, 50 mg., is given either by mouth or subcutaneously four times daily after meals and at bedtime for a period of four to six days.
3. Oxygen by double bent nasal catheter is inhaled, beginning with a flow of 1 L. per minute the first day and increasing by 1 L. per minute until 6 L. per minute are inhaled, representing 38 to 40 per cent oxygen. This is maintained for a period of one to four weeks, depending upon the clinical condition of the patient. When substantial relief of cough, dyspnea and expectoration has been obtained, the oxygen concentration may be gradually lowered in a similar fashion.[28]

With control of the refractory state, a program for maintenance therapy in the ambulatory patient has been devised. Instructions are explained and demonstrated to each patient before he leaves the hospital or, in the event treatment was administered at home, before he is allowed out of bed.

Directions for Patient with Pulmonary Emphysema

1. On arising, use the nebulizer promptly, inhaling Vaponefrin or (in some cases who are temporarily refractory to epinephrine), Isuprel, four times in deep inspirations.

2. Manually elevate the diaphragm, as directed, with the palms of the hands underneath the ribs, pushing upward and inward during the last half of expiration. This is to be done 10 times, leisurely, either in bed or sitting up.[29, 30]

3. The manual elevation of the diaphragm and Vaponefrin may in itself provoke coughing but, if not, coughing should be practiced deliberately to get up any mucus that might be present.

4. Aminophylline, 0.2 to 0.3 gm., or Kiophyllin, should then be taken with half a glass of water as directed, on arising and at 3 p.m.

5. Diaphragmatic breathing has recently been found to be of marked value in many cases of pulmonary emphysema.[29] Practicing at first lying down, with one hand on the abdomen and one on the chest, the patient should attempt to see that the abdomen protrudes forward during inspiration with little or no chest movement. After this has been carried out for two minutes, the same exercise should be undertaken sitting up and then walking.

6. The Burgess Gordon two-band belt should then be applied over the lower abdomen and worn for the rest of the day.

7. During the late afternoon, between three and five o'clock, or, if inconvenient at that time, before dinner, Vaponefrin should be inhaled again, followed by manual elevation of the diaphragm and by the exercises above described.

8. Before the patient retires, Vaponefrin should be inhaled again, followed by manual elevation of the diaphragm and an attempt to cough up whatever mucus may be present.

9. During the day, whenever exercise is attempted, the patient should endeavor to purse his lips while he is exhaling, so that he breathes against an obstruction deliberately introduced at the mouth. The breathing outward during expiration should be conducted slowly but should not be so unduly long as to provoke coughing. This expiratory pressure breathing should be employed during all exercise.[12, 26]

10. When sputa are very viscous and difficult to raise, potassium iodide should be taken three times daily before meals for two weeks on and one week off. Side effects, such as excessive nasal discharge, acneform eruption or swollen glands, may necessitate stopping this medication temporarily.

11. Intermittent inhalation of 70 per cent oxygen by Meter mask for 20 to 30 minutes two or three times daily is of value in diminishing weakness and dyspnea, and improving tolerance to exercise. The decrease in pulmonary ventilation aids in lessening the overinflation of the lungs.

12. Any acute upper respiratory infection, sinusitis or grippe should be treated promptly with antibiotics.

In addition to the breathing exercises reported by Livingstone [31] and abdominal belts [32, 33] designed to increase the efficiency of diaphragmatic respiration and aid in emptying the lungs more completely, the effect of pneumoperitoneum in the management of ambulatory patients with pul-

monary emphysema has been found helpful in some cases.[34, 35, 36, 37] Preliminary studies of pulmonary function and venous pressure following pneumoperitoneum in our clinic have been encouraging, and a decided improvement in tolerance of activity has been obtained in several patients. Additional data on the effect of pneumoperitoneum on the circulation will be presented in a subsequent paper.[38]

While the determination of the arterial oxygen saturation would serve to measure the degree of anoxemia present in the patient with emphysema, it is not entirely reliable as a guide for therapy. In clinical practice, many of these patients maintain an excessive pulmonary ventilation, with the result that the arterial blood is almost normally saturated with oxygen. A simpler and more useful test with respect to the efficacy of oxygen therapy, in use since 1938,[10] is the determination of the pulmonary ventilation while the patient breathes air and then 100 per cent oxygen. A fall in the pulmonary ventilation, accompanied by relief of dyspnea while breathing oxygen over a minute period seems to us a more satisfactory guide to the possible benefits of oxygen therapy.

The following case history has been selected as an example of the clinical improvement possible in a patient with severe ventilatory insufficiency due to pulmonary emphysema.

Case Report

A 55 year old white salesman was admitted to the hospital complaining of shortness of breath of four and one-half years' duration. For 12 years prior to his present illness he had suffered from repeated respiratory tract infections, during the course of which expiratory wheezes were occasionally heard. Dyspnea became gradually more severe and was accompanied by loss of weight but no cough, chest pain, orthopnea or peripheral edema. Three years before his admission, the diagnosis of pulmonary emphysema was made. Since then, although temporary relief was obtained by aminophylline and adrenaline by injection, the course of rapidly incapacitating dyspnea was not halted. Fluoroscopy and roentgenogram of the chest revealed marked flaring of the ribs, a low fixed diaphragm, increased aeration of both lung fields and a small, drop-shaped heart. Vaponefrin and Isuprel by nebulization gave temporary relief for the year prior to hospitalization. Activity gradually declined to the point where the patient was bedridden.

At the time of admission to the hospital, this severely dyspneic patient revealed a barrel-shaped chest: The respiratory movements were maintained by the upper intercostal muscles and the accessory musculature of the neck. The diaphragm was motionless. There were loud expiratory wheezes throughout both lungs. The vital capacity was 1,270 c.c., and the maximal breathing capacity 8,840 c.c. per minute, or 9.6 per cent of the expected normal value. The pulmonary ventilation while breathing 100 per cent oxygen was 34.6 per cent less than the value obtained when breathing air (5,720 c.c. per minute on 100 per cent oxygen, 8,750 c.c. per minute on air). One hour after breathing 100 per cent oxygen, the carbon dioxide content of the blood rose from 60.5 vol. per cent to 72.8 vol. per cent. During that time the pH dropped from 7.49 to 7.35. Pneumoperitoneum was induced by introducing 1,200 c.c. of air, raising the intraperitoneal pressure to plus 11 cm. of water. He was instructed to elevate his diaphragm manually 10 to 12 times, three times daily, and was trained in diaphragmatic breathing. The response to this regimen was striking. There was

an increase in the patient's vital capacity to 50 per cent (or 1,820 c.c.) of the expected value. The maximal breathing capacity increased to 14,700 c.c. per minute, or 16.1 per cent of normal. Administration of Vaponefrin caused a further improvement in the vital capacity to 2,230 c.c. and in the maximal breathing capacity to 20,600 c.c. per minute (61 per cent and 22.6 per cent of normal respectively). At the present time the patient is ambulatory and returns to the office at periodic intervals for refills of the pneumoperitoneum. The increase in activity tolerance has been accompanied by an optimistic change in the mental outlook.

Summary

In 21 patients with pulmonary emphysema, a significant fall in the resting pulmonary ventilation was observed while breathing 100 per cent oxygen. This decrease in the minute ventilation offered an explanation for the elevation in the arterial carbon dioxide concentration. Four patients in this group exhibited mental changes, accompanied by a marked increase in the arterial carbon dioxide tension and an acid shift in the blood pH. Analysis of previously published data, as well as the results of our own studies, would seem to indicate that respiratory acidosis is the critical factor in the alteration in mental function, rather than carbon dioxide retention without acidosis.

These studies confirm the desirability of a program of oxygen treatment in which the percentage of oxygen administered is gradually increased over a period of a week or 10 days in order to prevent respiratory acidosis and mental changes.

Spirographic studies following the oral administration of aminophylline indicate that this drug is of value in the treatment of bronchospasm in the majority of patients with pulmonary emphysema, provided it is administered on an empty stomach. An increase of 45.8 per cent in maximal breathing capacity was demonstrated one hour after ingestion in 15 patients. The beneficial results of inhalation of nebulized epinephrine, particularly 2.25 per cent synthetic racemic epinephrine, were confirmed in this study.

Various technics which tend to decrease overinflation of the lungs were described, including manual elevation of the diaphragm, pursed lip and diaphragmatic breathing, abdominal belts and pneumoperitoneum.

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PULMONARY MANIFESTATIONS OF MYCOSIS FUNGOIDES *

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MYCOSIS fungoides is a disease of the reticuloendothelial system. The disease manifests itself primarily in the skin, although visceral manifestations frequently occur. In 1935 Stuhmer [1] wrote: "The complications which appear in the lungs in the form of real mycosis tumors generally are not discovered during life." We have recently observed four cases of mycosis fungoides with the typical skin picture in which pulmonary infiltrations were found on roentgen examination. Three of the four cases were verified at autopsy. The fourth case had lesions in the lung on roentgen examination and clearing of these lesions following treatment with nitrogen mustard and radioactive phosphorus.

CASE REPORTS

Case 1. A 54 year old white man stated that five or six years previously a large scaly brown patch had appeared on the skin of the left anterior chest wall. This patch was asymptomatic and remained unchanged for six years. An itching lesion of the right anterior thigh then developed which became a tumor and subsequently ulcerated. Several dermatologists made a diagnosis of mycosis fungoides and treated him with a total of 1,800 r roentgen-rays to the ulcerated lesion of the right thigh. He then received 100 mg. of nitrogen mustard daily for four consecutive days at the Mayo Clinic, with only slight improvement. When seen again at the Mayo Clinic two months later, the ulcer on the right thigh had enlarged, and isolated infiltrated plaques had appeared elsewhere on the body. He was given a second course of nitrogen mustard therapy nine months later without appreciable improvement. A nonhealing ulcer of the right thigh was excised and a new lesion appeared at the margin of the excised lesion. At this time new infiltrated lesions began to appear on the trunk, scalp, face and neck. Histologic examination of several of these lesions revealed mycosis fungoides. Roentgen films of the chest at this time revealed bilateral nodular infiltrates compatible with specific pulmonary infiltrates. Radioactive arsenic was given intravenously, but this therapy was ineffective and in one month the pulmonary infiltrates grew so rapidly that the patient became dyspneic and was in acute distress. Deep roentgen-rays of approximately 700 r to the center of each lung were given, with dramatic subjective and objective improvement. A third course of nitrogen mustard was then given, with some improvement, particularly to the face lesions. The following month a decrease in the red blood cells occurred which required seven transfusions of whole blood. A sternal puncture at this time revealed an increase in the number of plasma cells. During the next several months

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new, extremely painful ulcerative lesions appeared on the scalp, face, neck, eyelids, back and anterior hip region.

Physical examination on admission revealed a fairly well developed, moderately well nourished man who appeared to be older than his stated age. On the skin there were numerous ulcerated lesions of purplish color, varying from several millimeters to 1.5 cm. in diameter and covering the entire body, particularly the scalp. There was a generalized disseminated formation of pigmented areas, nodules and ulcers. The pigmented areas and ulcers varied in size, shape and configuration. The nodules were of a purplish red color, rounded and firm but not hard, and varied from 3 mm. to 2 cm. in diameter. Many of the ulcers were discrete, rounded and punched-out, with a granulomatous base covered with a gray-white necrotic material. Other

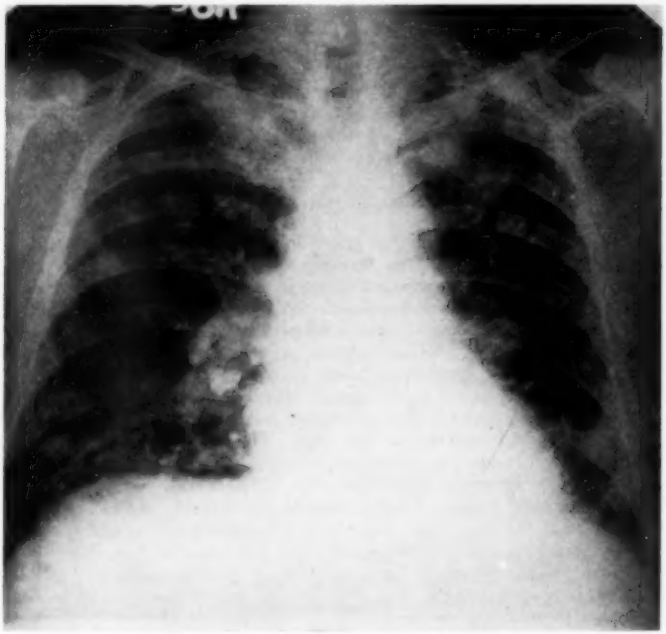

FIG. 1. *Case 1*, showing bilateral, nodular infiltrates.

ulcers had a definite rolled border and were crateriform in appearance. There was a pitting edema from the midline of the legs inferiorly, including the ankles and feet. The chest was symmetrical in appearance. There was a lag on the left side; and some dullness to percussion was noted on the lateral side of the left chest wall posteriorly. In the same area the breath sounds were increased, and posteriorly there were small moist râles. The chest appeared to have slightly less expansion on the left side. The physical examination was otherwise negative.

Laboratory Examinations:

Urine: Varied from essentially normal to a trace of albumin and 4 to 10 white blood cells per high power field, 4 to 8 red blood cells per high power field, and occasional waxy and granular casts and a few epithelial casts.

Blood:

Red blood cells ..... 3,050,000 to 3,720,000 per cu. mm.
Hemoglobin ..... 9.5 to 11.5 gm.

	2/15/49	2/17/49	2/23/49	3/1/49	3/7/49	3/10/49
White blood cells	7,900			17,300	29,950	31,000
Neutrophils, per cent	63			19	92	0
Lymphocytes	20			7	8	2
Eosinophils	14			8	0	7
Juveniles	3			15	0	5
Monocytes	0			3	0	0
Myelocytes	0			4	0	1
Band forms	0			44	0	4
Segmented forms	0			0	0	82
Blood platelets					150,000	
Sedimentation rate mm.		26				
Total protein		6.1	6.6		6.0	
Albumin			2.8		2.2	
Globulin			3.1		3.8	
N.P.N.					40.0	

Chest X-ray: 2/17/49: "There are blotchy densities scattered throughout all lung fields from apex to base. The hilar shadow and linear markings are accentuated. Fairly large calcific densities are seen along the right bronchial tree towards the base. Impression: The appearance of this chest is compatible with a pulmonary spread of mycosis fungoides, as reported in the clinical history." *2/28/49*: "When compared with the previous examination roentgenogram of the chest reveals an increase in the number and size of the blotchy densities scattered throughout all lung fields. In addition, there is a homogeneous density somewhat triangular in shape and its apex at the axillary margin of the second anterior rib on the left, with its base at the diaphragm and heart border. Impression: The pathologic lesions previously described have somewhat increased and, in addition, an encapsulated pleural effusion has formed in the left chest."

Course: The patient developed a progressive, generalized jaundice one week before death. The hair of the scalp and eyebrows was almost entirely absent. Cervical and axillary lymphadenopathy developed. He suddenly manifested confusion and disorientation, and a diagnosis of toxic psychosis was made. Diffuse subcutaneous hemorrhages, especially of the arms and forearms, appeared. He died one month after admission to the hospital.

Autopsy: Anatomic diagnoses (including histologic findings): (1) Mycosis fungoides, primary in the skin, with involvement of the lungs, liver, testes, stomach mucosa, spleen, bladder mucosa, pancreas and bone marrow. (2) Prostate, adenomatous hypertrophy. (3) Simple cyst of liver.

Lungs: On cut section of the lung, there are numerous nodules throughout the lung tissue which are discrete and vary in size from 7 mm. to 2 cm. They cut very hard and on cut section are yellowish gray.

Histology: Lung: Section shows one area which is not involved with infiltration in which the alveolar septa are very thin. Immediately adjacent to this there is an area of infiltration with very pale staining eosinophilic epithelioid-like infiltration containing numerous cells, called mycosis cells. The area immediately adjacent to this shows almost complete hyaline degeneration.

Case 2. A 58 year old white man stated that he had been well until 15 months previously, when his "bladder stopped up." He was treated with prostatic massage and sulfanilamide tablets. Two months later he noted flat red spots about the knees,

which rapidly spread to involve other areas and became generalized in two months' time. Some of these lesions were thickened and scaling and others formed nodules. The eruption had been nonpruritic. A physician then told him that he had "change of life," and treated him with hormones. He had noted weakness and malaise for five months, with hoarseness and difficulty in breathing for the past four months. There had been extreme weakness, malaise and pain in the joints of the fingers and

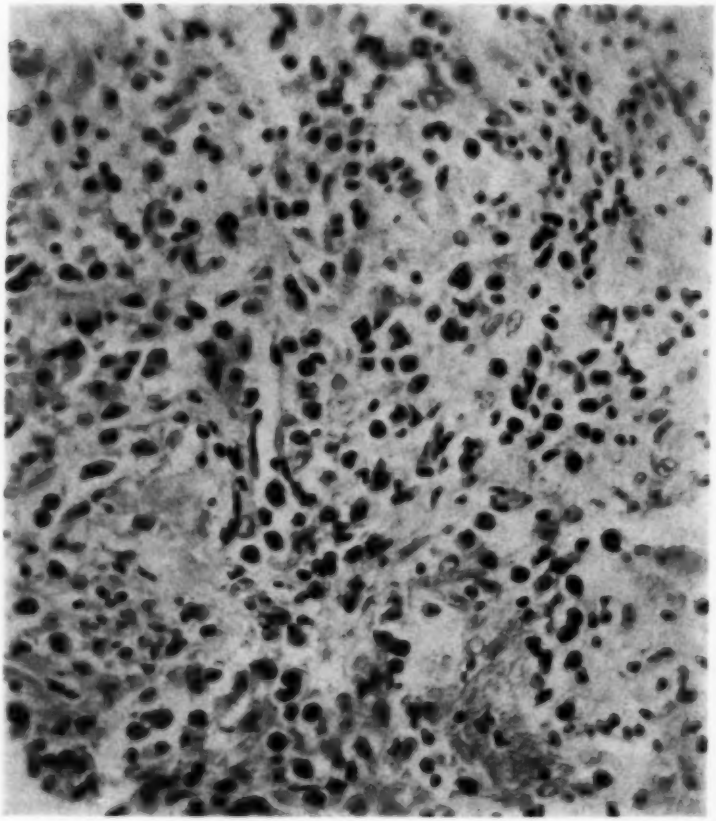

FIG. 2. Typical mycotic cells in lung tissue.

toes for the past five weeks. He had been hospitalized a month previously, and treatment had consisted of two blood transfusions and streptomycin—about 20 injections, according to the patient.

On admission the patient appeared to be seriously ill. He seemed somewhat lethargic and had extreme hoarseness and difficulty in phonation. There was also marked edema of the face, foreskin and scrotum, sacral area and upper and lower extremities. There was a generalized florid skin eruption, most marked on the ex-

tremities and face. The lesions were in all stages of evolution and involution, some being superficial, erythematous scaly plaques, some more infiltrated, and others rubbery, deep-seated nodules from bean to walnut size. There were gray-brown macules at the sites of preëxisting lesions, and scattered capillary telangiectases on the front and back of the thorax. The buccal mucosa, soft palate and uvula showed several crateriform ulcers measuring up to 5 mm. in diameter and 3 to 4 mm. deep. The anterior borders of the tongue were red and somewhat denuded.

Examination of the lungs revealed some questionable dullness over the right upper lung fields. There was a generalized lymphadenopathy, most marked in the axillae.

Laboratory Examinations:

Urine:	
Albumin	Trace to 3 plus
Microscopic	Few white blood cells and occasional red blood cells
Blood:	
Hemoglobin	14.5 gm.
Red blood cells	5,460,000 to 3,200,000 per cu. mm.
White blood cells	15,000 to 46,000 per cu. mm.
Neutrophils	91 per cent
Lymphocytes	7 per cent
Monocytes	2 per cent
Total protein	Consistently low
AG ratio	Reversed
Sputum	Many examinations negative for acid-fast organisms
Thymol turbidity	10 units
Alkaline and acid phosphatase	Normal
Serum bilirubin	Less than 0.5

Sternal Marrow: "Marrow is of average cellularity. The distribution of granulocytes and nucleated red appears normal. The neutrophils display marked toxic granulation. There are an unusual number of macrophages—significance unknown. Careful search of two slides revealed none of the so-called 'lupus erythematosus' cells."

X-ray of Chest: "The chest shows evidence of pulmonary infiltration. There is a small area of pleural fibrosis in the right apex, and thickening of the interlobar fissure on the right."

Surgical Biopsy: Lesion of left chest. The diagnosis was mycosis fungoides.

Treatment: Treatment was mainly supportive. He was given steam inhalations, three units of plasma, 500 c.c. of whole blood, crystacillin, 300,000 units intramuscularly every 12 hours, and vitamin E.

Course: After admission the patient's condition remained essentially unchanged except that the edema had increased and the red and white blood cell counts had decreased. There was respiratory obstruction, but examination of the larynx revealed that the epiglottis was normal and the pyriform sinuses were clear, with moderate edema of the arytenoid and marked edema of the false cords. The cords were uneven and covered with a white exudate. There was a small uneven nodule in the interarytenoid space. The airway was adequate. The patient developed a bloody diarrhea, and the respirations became more rapid and shallow and the pulse rate increased. He died 20 days after admission to the hospital.

Autopsy: Anatomic diagnoses (including histologic findings): (1) Generalized mycosis fungoides (lymphoblastosis) of the skin, liver, lung, adrenal, lymph nodes. (2) Multiple benign polyposis of descending colon. (3) Adenocarcinoma of the descending colon.

Histology:

Skin: The section through the skin revealed a somewhat increased amount of keratinization. The epithelial layer was infiltrated with large cells having clear cytoplasm and nuclei that are darkly staining. The cells ranged from dark round cell types to those of larger epithelioid character. Mitotic figures were only occasionally seen. In the deeper layers, nests of the same type of cells were seen around the sweat glands and blood vessels. In a few areas these cells were seen invading

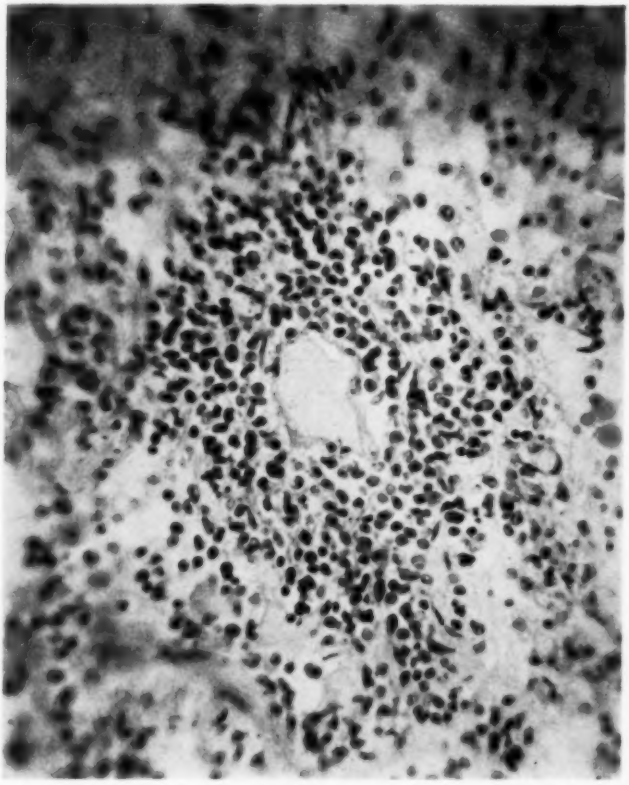

FIG. 3. *Case 2.* Lymphoblastic (mycosis fungoides) infiltration in the lung.

the lumen of the blood vessels. The larger cells resembled "mycosis cells." *Impression:* Mycosis fungoides.

Lung: The microsection revealed an extreme amount of congestion completely filling many alveolar spaces with serous exudate containing round cells, polymorphonuclears, and macrophages. There was also an increased hyperemic reaction. A number of alveolar spaces were distended and gave the appearance of compensatory emphysema. Around some of the smaller vessels, sheets of immature round

cells were collected. *Impression:* Bronchopneumonia of the lung with lymphoblastic infiltration.

Colon: The mucosa was polypoid in character. The mucous glands were engorged and the nuclei small and vesicular. An increased number of lymphocytes were seen between the glands. Throughout the submucosa there were many anaplastic epithelial cells arranged in acini, several of which contained mucus. Several other sections revealed benign polyposis formation. *Impression:* Adenocarcinoma of the sigmoid colon. Multiple polyposis.

Comment: This case is of further interest in that there was an associated adenocarcinoma of the colon. The association of carcinoma and mycosis fungoides is not common.

Case 3. A 51 year old white man was admitted with a diagnosis of mycosis fungoides. The past history revealed that 14 years previously he had developed a chronic, intermittent pruritus of the back. However, no lesions were noted until eight years later, when red blotches appeared on the right flank which increased in number and distribution. A biopsy was reported as showing mycosis fungoides. He was treated by a dermatologist with superficial roentgen-ray therapy and Asiatic pills for the next four years. He was then given treatment at several institutions with various medications, including nitrogen mustard.

Physical examination revealed a well nourished, ambulant and not acutely ill man. On the skin were many elevated, plaque-like erythematous lesions of the neck, trunk and extremities. The lesions tended to be discoid, with some tendency towards confluence, and the formation of bizarre configurations. Palpation of the lesions revealed them to have very definite tumor-like consistency. At times these lesions tended to break down and form weeping lesions with some crusting. The skin lesions were compatible with the admitting diagnosis of mycosis fungoides. There was a purulent lesion on the medial aspect of the right lower lid, with small plaque-like infiltrate. This granulomatous lesion was about 6 to 7 mm. in diameter nasally, and was considered to be mycosis fungoides of the right lower conjunctiva. The remainder of the physical examination was essentially negative.

Laboratory Examinations:

Urine: "Usually negative except for an occasional 1 plus albumin."

Blood:

Hemoglobin ..... "Within normal range"
Red blood cells ..... 3,000,000 to 4,500,000 per cu. mm.
White blood cells ..... 10,000 to 12,000 per cu. mm.
Differential counts ..... "Normal except for an eosinophilia up to 26 per cent"

Chest X-ray: Roentgenogram of the lung showed increased markings of the lung fields. There was "increased infiltration in the pulmonary fields."

Treatment: Generally supportive, and mainly directed against the pruritus; it consisted of skin lotions, occasional small blood transfusions and superficial roentgen-ray therapy to the involved areas of the skin. Deep x-ray therapy was later given but resulted in no marked improvement in the condition.

Course: The patient's course was downward. He became weak and had a progressive fever, and died 10 months after admission.

Autopsy: On gross examination there was widespread brown pigmentation of the skin, which was diffuse but in some areas darker, forming a net-like appearance. In addition, over the entire skin surface there were small, thickened, excoriated patches of skin, some of which were hemorrhagic, some ulcerated and some crusted. They varied from 2 or 3 mm. to 1 cm. in diameter, and were mainly on the forehead, cheeks, neck, forearms, trunk and lower extremities. Except for an occasional axillary and inguinal node, there was no significant lymphadenopathy.

Lungs: On section through the lung parenchyma, a severe degree of congestion was noted in the lower lobes and patchy areas of consolidation all through the parenchyma of the lower lobe. The outline of these areas was irregular and up to 1 cm. in the greatest diameter.

Histology:

Lung: Section from a lower lobe showed a marked degree of congestion which in a large circumscribed area was so intense that the process appeared to be a hemorrhagic infarction. The alveoli were completely filled with laked red blood cells, and the septal walls between alveoli were fairly recognizable. Nuclear structures were

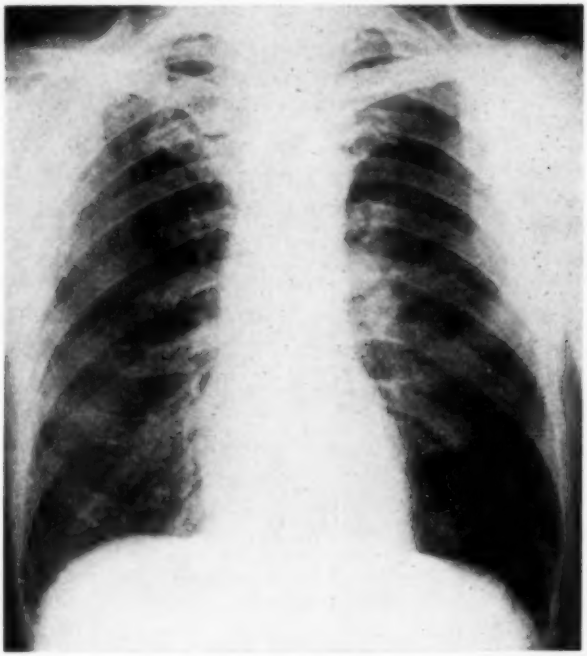

FIG. 4. *Case 3.* Increased markings in the lungs due to pulmonary infiltration of mycosis fungoides.

missing in these areas. The periphery of these areas of infarction revealed a recognizable pattern. The alveoli elsewhere were filled with a pink-staining edema fluid and occasional macrophages and a marked vascular infiltration composed of round cells.

Skin: Microsection from an ulcerated cutaneous lesion showed thinning of the covering epithelium, apparently due to invasion by a heavy infiltration of round cells which completely filled the upper layers of the corium. The skin surface was partially ulcerated and covered by a granular debris of fibrinoid material and disintegrating cells. The underlying tissue was heavily infiltrated with round cells identical to those underlying the intact epithelium. In the deeper layers of the corium, remnants of

sweat glands and blood vessels were seen, and there was a conspicuous perivascular infiltration consisting of lymphocytes. These lymphocytes were also cuffed about sweat glands. Two or three giant cells were seen, similar to those described in some of the lymph nodes and consisting of an oval mass of basophilic staining cytoplasm with two or three eccentrically placed nuclei. These were seen in the corium. The corium was quite vascular, due to an increase in small blood vessels and capillaries. There was a sharp line of demarcation between the corium and the underlying connective tissue, and the cellular infiltration was confined to the corium and epithelial layers.

Case 4. The patient was a 33 year old white man whose past history revealed psoriasis since the age of three years; for the past four or five years, occasional ulcers had appeared in the psoriatic lesions. Increased pigmentation of the entire body had begun to appear one and one-half years before. He consulted a dermatologist, who made a diagnosis of psoriasis. Infiltrated plaques developed in the psoriatic lesions and a biopsy showed mycosis fungoides. He was treated for three days with nitrogen mustard therapy but the condition did not improve. He developed a leukopenia, and new fungating, ulcerating lesions of mycosis fungoides continued to appear. The patient was given ultra-violet irradiation and showed marked improvement. However, numerous fungating, ulcerating lesions again appeared, and there was no response to adequate roentgen-ray therapy. Examination of the sternal marrow and lymph node biopsy gave normal findings at that time. There had been a weight loss of 27 pounds in the past five weeks. He had a cough with expectoration two months previously, but this had cleared up after about one month. Other pertinent finding in the past history was a peptic ulcer of three years' duration.

Physical Examination: The skin showed generalized deep pigmentation, somewhat mottled and with a bluish tinge. There was no particular difference in the pigmentation on the exposed or covered parts of the body. There were psoriasiform lesions with thin, silvery, loosely attached scales on an erythematous base, with little or no infiltration, on the extremities and trunk. The lesions were not limited to the extensor surfaces. They were from coin to palm size. On the forehead, trunk and extremities were coin-sized, circular, fungating lesions with a keratotic surface. On the shoulders, sternocleidomastoid region, back, pelvis, thighs, knees and legs, particularly on the left hip and right forearm, were larger arciform, circinate, irregularly shaped infiltrated areas, some of which were ulcerated exposing a purulent pink base. These punched out ulcers were sharply marginated and from 4 to 8 mm. deep.

Examination of the lungs revealed soft coarse râles over the upper one-third anteriorly and posteriorly. Examination of the abdomen disclosed deep tenderness about the umbilicus. There were varicosities of the right scrotum and of both legs.

Laboratory Examinations:

Blood Count:	7/28/50	8/28/50	9/11/50
Red blood cells	4,900,000	4,120,000	4,080,000
Hemoglobin	14.1	13.0	12.5
White blood cells	6,950	11,500	9,100
Polymorphonuclears	1%		2%
Segmented	73		70
Eosinophils	2		2
Basophils	0		0
Lymphocytes	18		23
Monocytes	6		0
Toxicity	Plus		
Sedimentation rate	40		30
Blood platelets		359,920	326,000

Bone Marrow: "Normal bone marrow."

Tuberculin Test:

.0005 mg. PPD (Second strength) ..... Negative
0.1 c.c. 1:1,000 Histoplasmin ..... Negative
0.1 c.c. 1:100 Coccidioidin ..... Negative

X-ray Examinations: 7/28/50: Questionable shadow in left first interspace. Mediastinum not enlarged. 7/31/50: Small rounded areas of increased density in left lung level of the first rib, fourth rib and in right upper lung field. Interpreted as possible leukemic infiltrates. 8/28/50: Rounded areas in chest unchanged. 9/11/50: Chest improved since previous examination. Definite densities present but indistinct. 9/20/50: Further improvement since last examination.

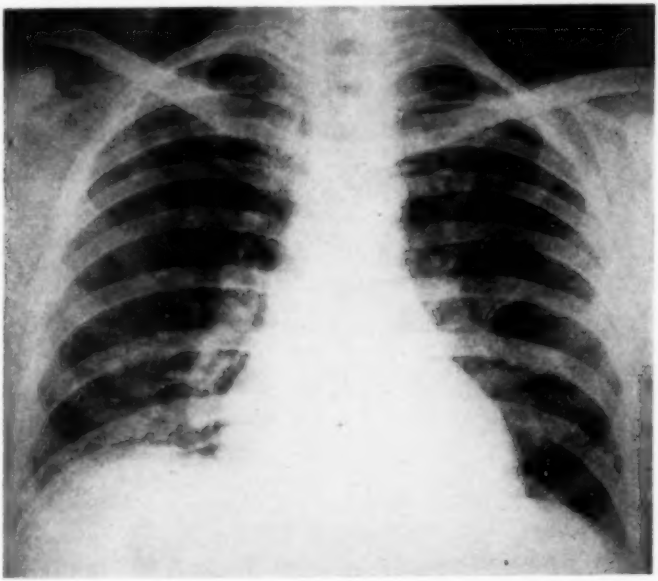

FIG. 5. *Case 4.* Small rounded parenchymal infiltrates scattered through both lung fields.

Treatment: ACTH was given for four days, 25 mg. four times daily. Nitrogen mustard was given for four consecutive days, one ampule in 500 c.c. saline. This treatment produced nausea. Two treatments with P^{32} were given, the first of 4 mc. and the second of 4.29 mc. No benefit was noted so far as the skin lesions were concerned. Cortisone was given for a period of 14 days, starting with 50 mg. daily and increased until 200 mg. were given on the last day. This treatment was felt to be of definite benefit to the skin lesions, and was supplemented by ultra-violet irradiation to selected areas. All the areas improved.

Course: The patient ran an intermittent fever with daily afternoon rise in temperature throughout the hospital stay, except while on cortisone therapy and for a short period thereafter. The skin lesions did not respond to ACTH, nitrogen mustard or P^{32}, but did improve while on cortisone and ultra-violet irradiation.

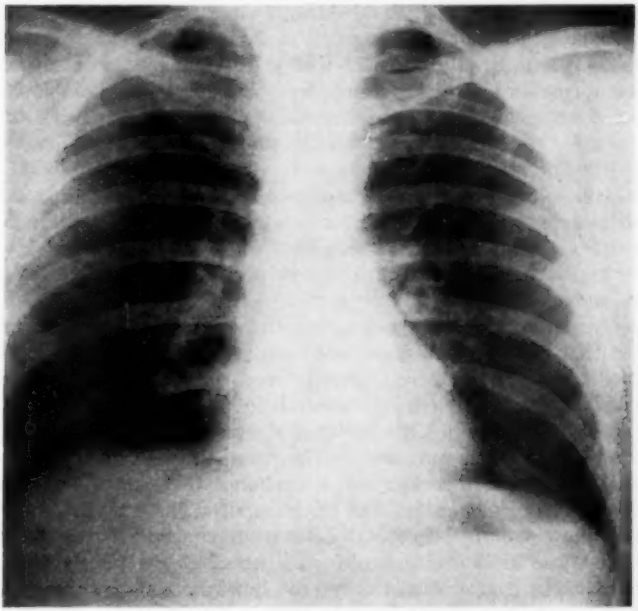

FIG. 6. Regression of pulmonary lesions after treatment with radioactive phosphorus and nitrogen mustard.

Comment: This case is of interest for two reasons. First, the association of psoriasis with mycosis fungoides and, second, the response, as demonstrated by roentgen examination, of the pulmonary lesions to nitrogen mustard and radioactive phosphorus.

COMMENT

Following Paltauf's [2] review of mycosis fungoides in 1909, the belief that involvement of the internal organs was rare became widely accepted. This view is emphasized in current publications and textbooks, although complete review of the subject would confirm the fact that there is no basis for this opinion, according to Berman.[3] Twenty-two proved cases showing involvement of the internal organs reported from 1895 to 1927 were collected by Liechti.[4] He reported two additional cases, and concluded that Paltauf's dictum was erroneous. Seventy-four cases were studied by Sequeira,[5] who concluded that involvement of the internal organs was common. The reports of 60 cases of mycosis fungoides recorded from 1928 to 1938 were collected by Berman.[3] While autopsy was done in only 30 per cent of the cases, it is notable that in 16 of the 18 cases examined there was involvement of the internal organs. The spleen, liver and lungs were the organs most frequently involved, while the intestines were involved in five cases and the

adrenals in four cases. It was Berman's conclusion that involvement of the internal organs in mycosis fungoides is the rule rather than the exception. This is in agreement with Curtis,[6] who stated that in each of 10 cases of mycosis fungoides in which autopsy was performed he was able to show that the disease had not been cutaneous alone but had involved many internal organs. Support is given Cottini's [7] view that the unknown factor causing the different aspects of mycosis fungoides acts electively on the reticuloendothelial system, and is capable of provoking the diffuse and generalized picture of the systemic form as well as the circumscribed localized manifestations familiar to dermatologists.

The first writer to mention involvement of the lungs in association with mycosis fungoides was Breakey [8] in 1902. In a case reported by Roman,[9] histologic examination of the lung nodules revealed the cells to be so crowded together that the lung structure was unrecognizable. This is similar to our third case reported here. Detailed reports of two cases of mycosis fungoides with very extensive visceral involvement were recorded by Paltauf and von Zumbusch.[10] Both cases showed involvement of the lungs with tumors of mycosis fungoides. The roentgenologic changes in mycosis fungoides were first described by Kuznitsky.[11] He termed his findings "speckled streakings" or "implied streakings." The lung changes in his case were not demonstrable clinically, but roentgenologically showed changes similar to those in Boeck's sarcoid. In two cases the lung changes were marked. There was a shadow over the lung area, the apices were clear and there was accentuation of the bronchial tube shadows. There was no evidence of inflammatory change. The von Pirquet test was negative. Thirty-one cases of mycosis fungoides with roentgen-ray findings were collected from the literature up to 1940 by Werth.[12] In most of these cases it was merely stated that "streaking" of accentuated hilar markings was present. He added two of his own cases in which roentgenograms were repeated after one year. In both cases the hilar shadows were enlarged, and extending from these regions into the lungs were linear and spotty shadows. Reëxamination revealed accentuation of the signs in both cases. Since the picture suggested Boeck's sarcoid, material from the tumors was inoculated into guinea pigs and rabbits, with negative results.

Other cases of pulmonary involvement in mycosis fungoides include that of Kovacs.[13] His patient was an 18 year old girl who developed mycosis fungoides at the unusual age of 11 years. She presented severe cutaneous manifestations and typical pathologic and histologic lesions in both lungs which were proved roentgenologically five months before death. The diagnosis was confirmed at autopsy. A case of mycosis fungoides with metastases as polymorphous cell sarcoma and involvement of the lungs was reported by Hemmingson.[14] Berggren [15] found pleural involvement in two cases and lung involvement in two cases in a total of 48 cases of mycosis fungoides. A case reported by Arzt [16] showed roentgenologic pulmonary findings which were interpreted as mycosis fungoides nodules. The case

described by Howles and Connell [17] exhibited diffusely distributed nodules on the surfaces of both lung lobes; the larger nodules measured 4 cm. in diameter and were of a deep red color, vascular and very friable. Autopsy specimens of a skin nodule from the abdominal wall and one from a metastatic lung lesion proved to be identical histologically. The lung was invaded by nodular formation without complete destruction of the alveolar wall, which is, however, usually seen in the advancement of malignant growths. In this case, the tumor seemed rather to infiltrate and widen the interalveolar spaces. A boy, aged 17 years, is reported by Portnoy.[18] He was well until one month before examination, when he noted a "lump in the skin" over the upper part of the sternum. It was first pink in color, and the patient believed the lesion was "going to be a boil," but in a week the color had become darker and the size had increased. Similar swellings, which underwent the same changes as the original sternal tumor, then appeared over the entire body, excepting only the arms, soles and scalp. The case was remarkable for the rapidity of the fatal course. The masses demonstrated in the lungs were presumed to be secondary deposits. The first case of Godel [19] was a 39 year old man in whom mycotic lesions were found in the lungs, pleura, mediastinum, tracheal mucosa, epicardium, soft palate, skeletal musculature and lymph nodes at autopsy. The second case reported by Paltauf and Scherber [20] was a 30 year old woman in whom mycotic infiltrations of the lung, heart, walls of the stomach and uterus and right oculomotor, trigeminal and femoral nerves were demonstrated at autopsy. The most complete publication regarding the roentgen-ray findings was that of Greifenstein.[21] His case was the first published with roentgen-rays, and he described the findings as "many almost round coarsely speckled shadows." The diagnosis was confirmed at autopsy.

The typical roentgen-ray picture of mycosis fungoides of the lungs is summarized by Werth [12] as follows: The lesion begins with hilar enlargement, which is not characteristic, followed by spreading of the affection along the vessels and manifested roentgenologically by increased streakings. Later tumorous changes occur, small nodules appearing along the vessels and bronchi so that the picture resembles bronchopneumonia or lymphangitis carcinomatose. These changes are characteristic in that the apices remain free until the end, markedly different from the picture seen in tuberculosis. Paltauf [2] was the first to demonstrate the initial symptom of organic mycosis fungoides as being perivascular. Unna [22] discovered that the lungs, while appearing normal on macroscopic examination, showed marked perivascular changes when examined microscopically. He considered these changes to be early mycosis fungoides, and Bennek [23] confirmed this by similar findings in other organs. These increased perivascular changes appear as ever-increasing streakings, according to Werth.[12] We know that lung involvement is always associated with a generalized lymph node involvement. One must imagine the path of infection as follows: The infectious agent enters the blood stream through the skin, lungs, etc., is caught in the lymph nodes

and does not enter the lungs until the breakdown of the hilar lymph nodes. This is confirmed by the fact that there is in all cases a hilar swelling, and that the apparent beginning of the lung involvement is observed near the hilus, according to Martinstein.[24] It is interesting that the lung findings closely parallel those of Boeck's sarcoid, and that in both diseases there is a positive anergy to the tuberculin test.

Summary and Conclusions

Little consideration has been given to the possibility of lung involvement in mycosis fungoides. The literature on mycosis fungoides rarely mentions lung roentgenograms, so it can be assumed that few films are taken of patients with mycosis fungoides or that there are no positive findings.

We have reported four cases of mycosis fungoides in which pulmonary lesions were demonstrated on roentgen examination. In three of the four cases this was verified at autopsy. The fourth case showed clearing of the pulmonary pathology following nitrogen mustard and radioactive phosphorus.

In one (case 2) there was an associated adenocarcinoma of the colon. In case 4 the patient had psoriasis in addition to mycosis fungoides.

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CASE REPORTS

AURICULAR INFARCTION: REPORT OF TWO CASES*

By Anthony J. Di Ielsi, M.D., Harry A. Pinsky, M.D., and Harold K. Eynon, M.D., F.A.C.P., *Camden, New Jersey*

The subject of atrial infarction has been recently reviewed by H. K. Hellerstein.[1] We are presenting two cases of auricular infarction which are of interest in several respects. One patient developed an infarct in the posterior wall of the right auricle, with mural aneurysm formation, resulting in dysphagia and eventual cardiac tamponade. In the second case, an elevation of the P–Ta segment was noted in the patient's electrocardiogram. The only other case we have been able to find in the literature showing the same electrocardiographic finding was the case reported by H. K. Hellerstein in the September, 1948, issue of the *American Heart Journal*.[1] This elevation of the P–Ta segment in Leads II and III is similar to the elevation of the S–T segment observed in these leads in recent ventricular infarction. Although neither of these cases was diagnosed ante mortem, auricular infarc ion was suspected in both, particularly in the latter case.

Case Reports

Case 1. A 67 year old white male was admitted to West Jersey Hospital on April 23, 1949, with the chief complaint of dyspnea and weakness. For two months previous to his admission the patient had been complaining of dyspnea with mild exertion and marked sweating. On the day of admission he experienced marked "tightness" in the precordial area, associated with dyspnea, sweating, weakness and collapse. Nausea and vomiting were also associated with the continuing precordial distress.

His past history included an episode of "rheumatism," which was considered mild, at the age of 31, and an attack of right-sided pleurisy in 1948. His habits were good and the remainder of the history was noncontributory.

On admission the patient presented the picture of an acutely ill, obese, dyspneic male. His blood pressure was 90 mm. Hg systolic and 60 mm. diastolic. Pulse rate was 112, and weak in volume. Respirations were 26 and somewhat labored. The pupils were equal and reacted to light and accommodation. There was no neck vein distention. The heart sounds were normal, and there were no audible murmurs. The lungs were resonant. All peripheral pulses were palpable. The liver, kidneys and spleen were not palpable. The hemoglobin content was 13 gm., the red cell count 4,200,000, and the white cell count 8,000. The sedimentation rate was 8 mm. in 60 minutes; the prothrombin time was normal. The urine showed a trace of albumin.

A diagnosis of acute myocardial infarction was made clinically, and the patient was treated with oxygen, papaverine, Dilaudid, aminophylline and Dicumarol. The electrocardiogram on admission was suggestive of a small posterior wall myocardial

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From the Department of Medicine, West Jersey Hospital, Camden, New Jersey.

infarction. The patient responded well except for a bout of hematuria four days after the inauguration of Dicumarol therapy. Dicumarol was permanently stopped and there was no return of urinary bleeding. An electrocardiogram taken on April 24 (figure 1) was reported as showing evidence of a disease state of the auricular myocardium. On May 18 the patient was discharged as improved after having spent 26 days in the hospital.

This patient was at home for an interval of seven weeks. He responded very slowly, and when seen on June 30 1949, was in cardiac decompensation. He was digitalized on that day and given an injection of a mercurial diuretic. Three days later he started to cough and to expectorate bright red blood. He complained this time of malaise, anorexia, nausea and vomiting. The hemoptysis became worse and the patient was readmitted to the hospital on July 9.

On his second admission, the blood pressure was 104 mm. Hg systolic and 86 mm. diastolic, pulse 92, respirations 22, and temperature 98.6° F. The entire left chest showed numerous coarse râles and many rhonchi, both anteriorly and posteriorly, and especially over the left apex. The right chest was essentially negative except for some emphysematous change. The heart was not enlarged clinically. There was a Grade I blowing systolic murmur at the aortic area with transmission into the vessels of the neck, and a grade II systolic murmur at the apex transmitted to the left axilla. The force, rate and rhythm were normal. The liver was palpable 3 cm. below the right costal margin and was somewhat tender. The spleen and kidneys were not palpable. There was no evident peripheral edema. "X-ray of the chest showed right-sided cardiac enlargement with posterior extension. The aortic arch was prominent and there was extensive mottling of the entire left lung, more marked in the upper and midpositions, as well as coarse mottling at the right lung base." A diagnosis of coronary heart disease with congestive heart failure and pneumonitis of the left lung was made. The patient's treatment included Digoxin, aminophylline, penicillin, streptomycin, aureomycin and Synkamin, together with repeated transfusions.

In spite of vigorous treatment, the patient's hemoptysis persisted and he continued to move steadily downward. The hemoglobin, which was 9.5 gm. on admission, dropped to 5.6 gm. within a week despite repeated transfusions; 8,500 c.c. of whole blood and 500 c.c. of blood plasma were given during the illness. A battery of hematinics was also given, but it was never possible to raise the hemoglobin above 10 gm. All blood chemistry studies and sedimentation rates remained within normal limits. The venous coagulation time was three minutes, the bleeding time one and one-half minutes.

An electrocardiogram taken at the second admission was essentially the same as the previous tracings except for the presence of digitalis effect.

On August 2, 1949, seven days before the patient's demise, he complained of dysphagia for solid foods. It was felt that the patient's general asthenia was responsible for this complaint, but as this dysphagia became progressively worse an extrinsic obstruction due to aneurysmal dilatation was considered. Roentgen-ray studies were ordered for August 10. On August 9, the patient suffered a sudden severe attack of dyspnea associated with dull aching pain in the right lower chest and marked sweating with a cold and clammy skin. Blood pressure was 90 mm. Hg systolic and 40 mm. diastolic; pulse was 112, and almost imperceptible. Respirations were rapid, shallow and labored. It was felt that this patient had had a massive pulmonary embolism, and oxygen and other measures directed toward its treatment were immediately instituted. The patient failed to respond, and died four hours after the onset of the acute attack.

Necropsy Findings: Patient was an obese, elderly white male with an emphy-

sematous type of thorax, facial cyanosis and moderate icterus, but with no visible evidence of edema. The pleural spaces were obliterated by moderately dense fibrous adhesions. The lungs were normal in shape and contour, and of a deep plum color. Their consistency was markedly increased. On cut section, the parenchyma appeared dark red and hemorrhagic; there were multiple pulmonary emboli filling practically the entire vascular tree of both lungs. The right lung weighed 1,280 gm., the left

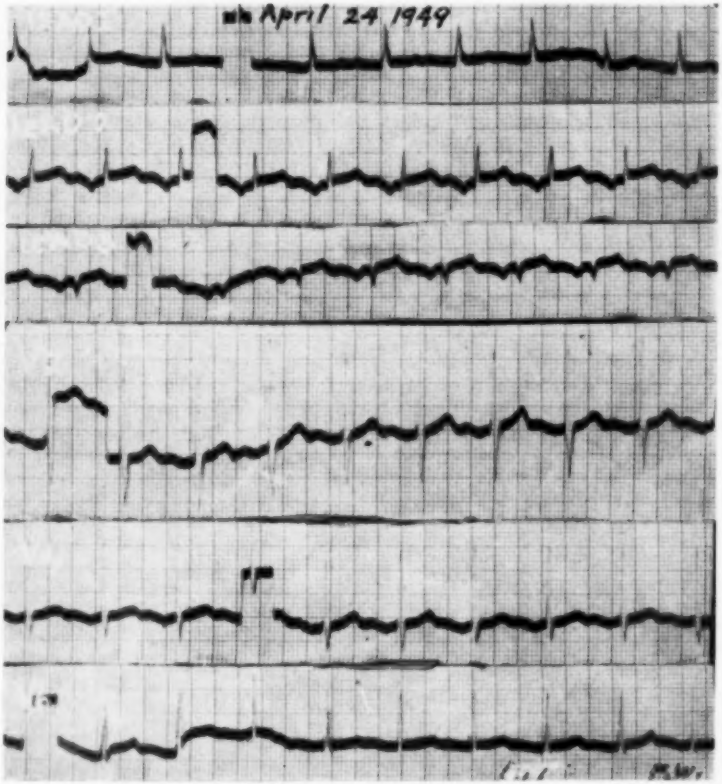

FIG. 1. *Case 1.* Note complete negativity of the P wave in Leads II, III, V_3 and V_4. P_1 is essentially isoelectric, and what appears to be a P wave in this lead is actually a U wave. The P wave abnormality as seen here was present in all of the tracings taken of this patient during his three and one-half months' illness.

1,220 gm. The pericardium contained about 300 c.c. of free fluid blood, and was adherent to the reflections of the great vessels to the right auricle and to the apex of the left ventricle. The right auricle was markedly dilated, extending superiorly and posteriorly. On closer examination it seemed to have formed an aneurysmal sac with multiple smaller component berry-like sacs. Cut section revealed a large, partially laminated mural thrombus filling the entire right auricle, auricular ap-

pendage and the smaller accessory dilatations described above. The superficial portions consisted of fluid blood which appeared to be leaking out through the small berry-like aneurysms. The endocardium and myocardium were mottled yellow, thrush-breastlike, and somewhat friable. The coronary vessels were markedly sclerotic throughout but with no specific thrombosed area observed. The heart weighed 550 gm. Examination of the esophagus showed no significant findings. However, the stomach wall was somewhat hyperemic and even hemorrhagic. No bleeding zones were observed. The liver weighed 2,250 gm. and appeared normal in shape and contour; it was yellowish-brown and studded with dark hemorrhagic spots, some of which showed central umbilication. On section, the portal vessels showed multiple thrombi loosely adherent to the intimal surfaces. The spleen weighed 650 gm. and externally appeared deep purple. On cut section, the parenchyma appeared deeply congested and the pulp scraped with ease. The right kidney weighed 150 gm. and the left 190 gm.; the capsules stripped with ease, leaving a dusky red, finely granular surface. On section, the ratio of cortex to medulla was somewhat decreased. The vessels of the boundary zone were moderately prominent. The remaining abdominal organs showed no significant pathologic changes.

Microscopically, sections of the lungs showed considerable hemorrhage in the alveolar spaces, with thickening and congestion of the alveolar walls. The pulmonary arteries and arterioles were filled with thrombi, some of which were undergoing recanalization. The remaining pulmonary parenchyma showed marked serous exudation into the alveolar spaces. Fatty changes were noted throughout the ventricular endocardium. There was marked narrowing and subintimal cholesterol deposition in the coronary vessels. The medial coat also showed fibrosis and reduplication of the elastic lamella. No vascular thromboses were seen.

The right auricular endocardium was markedly necrotic; the individual myocardial fibers were indistinct; there was loss of cross-striations, with infiltration of polys and lymphs throughout. A large laminated hyalinizing thrombus was attached to the endothelial surface and appeared to be undergoing organization.

The liver contained multiple areas of hemorrhage and necrosis, with loss of cellular outline. In some regions, well-demarcated from adjacent hepatic tissue, there was an infiltration of fibrous elements and mononuclear cells. Many hepatic cells contained a deep-brown pigment, probably hemosiderin. The spleen showed marked congestion of the sinusoids, with atrophy of the Malpighian bodies. The central arterioles were narrowed and showed sclerotic changes. Similar changes were seen in the arterioles and arteries of the kidneys. The collecting tubular epithelium showed marked cellular edema and loss of nuclear detail in many areas, somewhat suggestive of a lower nephron destructive process. Sections of the prostate showed a well defined nodular hyperplasia. There was moderate lipoidal depletion of the adrenal cortices. The pancreas showed some fatty infiltration.

Final pathologic diagnoses were: (1) Coronary sclerosis, marked, right posterior descending and left anterior descending arteries. (2) Right auricular infarction. (3) Right auricular aneurysm, with multiple concomitant berry-like aneurysms. (4) Cardiac tamponade. (5) Mural thrombus formation, right auricle and appendage. (6) Pulmonary embolism, multiple, with bilateral pulmonary infarction. (7) Portal thrombosis, with associated multiple hepatic infarctions. (8) Chronic passive congestion of the liver, lungs and spleen. (9) Necrobiosis involving renal tubules, etiology unknown. (10) Fatty changes in liver, lungs and spleen. (11) Icterus, moderate.

Case 2. A 69 year old white male was admitted to West Jersey Hospital on October 28, 1949, with the chief complaint of an oppressive sensation in the epigastrium. An hour previous to admission, the patient had experienced a "heavy,"

oppressive, dull, gnawing ache in the epigastrium, which quickly radiated to the precordium and thence to the medial surface of the left arm. Attendant findings were dyspnea, cyanosis and collapse. The patient was promptly brought to the hospital.

The past history was not contributory except for urinary symptoms during the previous year, suggestive of prostatism. His habits were good.

On admission, the patient presented a picture of an acutely ill, dyspneic, elderly white male, in shock and sweating profusely. His blood pressure was 68 mm. Hg systolic and 48 mm. diastolic. Pulse rate was 48 and weak in volume. Respirations were 32 and labored. The temperature was 98° F. rectally.

The pupils were equal and reacted to light and accommodation. There was no distention of the neck veins. The heart was clinically negative, except for the presence of a bradycardia. The lungs appeared clear; the chest was emphysematous. The liver, kidneys and spleen were not palpable. There was no peripheral edema. Rectal examination revealed a Grade III prostatic hypertrophy, with suspiciously hard nodularity of the right lobe.

A diagnosis of acute myocardial infarction was made. Electrocardiographic findings (figure 2) were confirmatory and showed changes diagnostic of the early phase of a recent posterior wall myocardial infarction. An associated auricular infarction was also suspected electrocardiographically. The patient was treated with oxygen, papaverine and Dilaudid, and dicumarolization was started. Anuria developed, however, and shock deepened. Treatment directed towards relief of the anuria failed; the patient gradually became comatose and died two days after admission.

Necropsy Findings: Patient was a very obese, 69 year old white male with no external marks of trauma, edema or jaundice. Examination of the pleural cavity revealed rather dense fibrous adhesions at the apex of the right lung. There was a minimal amount of fluid present in both pleural cavities. The thorax and viscera were in their normal relationships. The lungs showed marked acute passive congestion at the bases, with edema in both upper lobes. The right lung weighed 560 gm. and the left lung 550 gm. The pericardium revealed a minimal amount of fluid (40 c.c.) There were strands of fibrin on the surface of the heart and pericardial cavity. A fibrinous exudate with several areas of hemorrhage was observed on the posterior wall of the left ventricle near the septum. The heart was enlarged, with associated left ventricular hypertrophy. There were minimal sclerotic changes in the mitral and aortic valves. The right auricular appendage was hyperemic, and a mural thrombus was attached to its wall. An acute myocardial infarction, characterized by necrosis, hemorrhage and loss of normal myocardial pattern, involved the posterior wall of the left ventricle, right auricle and the septum. The coronary arteries were opened by multiple transverse section, showing the circumflex branch of the left coronary artery to be occluded by a thrombus and an atheromatous plaque about 2 cm. from its origin. The heart weighed 450 gm. There was a minimal amount of fluid in the peritoneal cavity. An excess of fat was observed in the mesentery and omentum. The liver was somewhat enlarged, weighing 1,730 gm.; on section it had a nutmeg appearance, with associated fatty changes. The gall-bladder showed no abnormalities; the bile ducts were patent throughout. The capsule of the spleen was somewhat thickened, and on section there appeared to be a marked increase in the fibrous tissue elements. The splenic pulp appeared somewhat soft and degenerated. The spleen weighed 110 gm. There were many hard, enlarged, matted preaortic and iliac nodes. The external surface of both kidneys was coarsely granular. Both pelves showed an increase in pelvic fat. The cortical substance was irregular,

grayish-pink in color, and somewhat diminished in amount; the vascular markings were very prominent. The ureters were patent throughout. The bladder wall was trabeculated and hypertrophied. The prostate was markedly hypertrophied, nodular and firm, and encroached on the left side of the urethra. The right and left kidneys weighed 150 gm. each. Genitalia were normal except for a hemorrhagic exudate discharging from the anterior urethra. The remaining abdominal organs showed no significant pathologic changes.

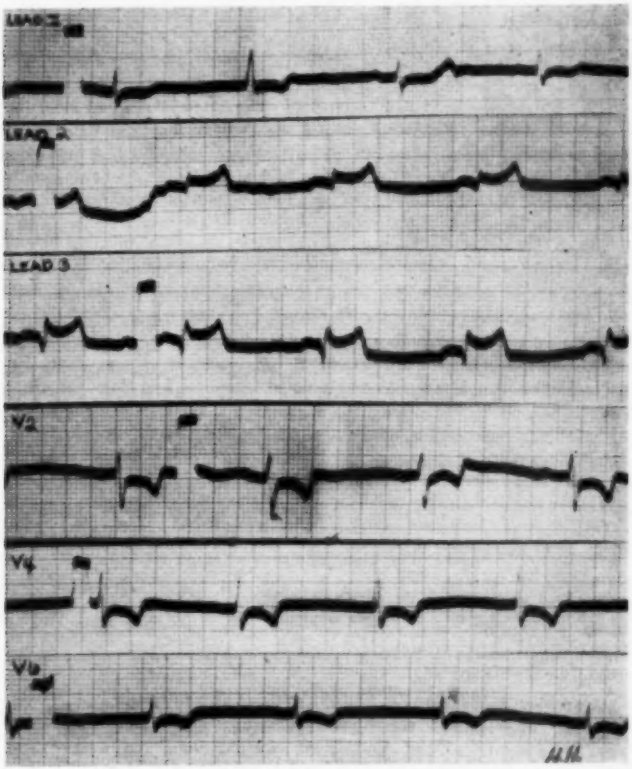

FIG. 2. *Case 2.* Note upward displacement of the P–Ta segment in limb Leads II and III.

Microscopically, sections of the heart showed the myocardium to be infarcted in many areas. The auricular and ventricular areas described grossly showed focal and diffuse fibrotic replacement, associated with increased vasculature, cloudy swelling and edema throughout. There was also evidence of polymorphonuclear, lymphocytic and monocytic cell infiltration between the necrotic myocardial fibers. The mural thrombus showed areas of beginning organization but was also characterized by lamination. The coronary vessels showed rather moderate to marked subintimal

arteriosclerotic changes, with cholesterol deposition, medial necrosis and the presence of recent and old vascular thrombosis. The latter, however, had not recanalized. The lungs showed marked thickening of the alveolar walls, and many of the alveolar spaces were completely filled with eosinophilic staining masses containing numerous heart failure cells. Other sections showed peribronchial and alveolar infiltration with monocytes and plasma cells, and occasional lymphocytes and polymorphonuclears. Also present were focal hemorrhages into the alveolar interstitial spaces. Sections of the kidneys showed areas of tubular epithelial degeneration with associated cloudy swelling. The glomerular tufts were thickened, partially hyalinized and fibrotic. The small and large vessels showed moderate to marked subintimal deposits of lipoid material, with associated fibrosis and luminal narrowing. The splenic parenchyma showed marked congestion, with no thickening in trabeculae and no marked diminution in the white pulp. Sections of the liver showed marked central necrosis of the hepatic lobules, most marked around the central vein and the adjacent liver cells. The periportal sinusoids were relatively uninvolved. The individual liver cells in the central portion of the lobule showed marked necrotic changes, while those in the distal portion showed evidence of cloudy swelling and congestion. The portal triad area contained multiple collections of chronic inflammatory cells. The prostate showed marked loss of normal cellular outline and definite infiltration into adjacent stroma, suggestive of malignant changes. Sections of some of the abdominal and periaortic nodes showed infiltrating acini replacing the normal lymph node architecture, possibly from the prostate.

Final microscopic diagnoses were: (1) Coronary thrombosis involving the circumflex branch of the left coronary artery, approximately 6 cm. from its origin. (2) Myocardial infarction, recent, involving the septum and the posterior wall of the left ventricle and right auricle. (3) Mural thrombosis of right auricular appendage. (4) Chronic passive congestion of the lungs and spleen. (5) Central hepatic lobular necrosis, with associated fatty changes. (6) Adenocarcinoma of the prostate. (7) Metastases from carcinoma of prostate to periaortic abdominal lymph nodes. (8) Benign nephrosclerosis, moderate.

Conclusions

Two cases are reported in which auricular infarction was a predominant finding. The first was of interest because of its clinical course, and the huge mural aneurysm of the right auricle found at the postmortem examination. The presence of this aneurysm was probably responsible for the dysphagia this patient suffered two or three days prior to his death. The multiple pulmonary emboli most likely originated from the thrombus in the right auricle. The terminal event was the rupture of this aneurysm, with cardiac tamponade and death. In the second case, the patient's clinical course was very brief but is reported because of the striking electrocardiographic findings. This patient suffered an acute myocardial infarction involving the posterior wall of the left ventricle, right auricle and interventricular septum. The elevation of the P–Ta segment in Leads II and III offered a clue to the presence of a recent infarction involving the posterior wall of one of the auricles. The rarity of this finding in the electrocardiographic literature has already been noted, and it was felt that it would be of interest to report this entity at this time.

ACKNOWLEDGMENTS

The authors would like to express their appreciation to Dr. William R. Platt for the pathologic report, and to Dr. William Most for the clinical case histories of the patients.

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ANOREXIA NERVOSA TREATED BY PREFRONTAL LOBOTOMY *

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THIS paper deals with a refractory case of anorexia nervosa treated by prefrontal lobotomy.

Anorexia nervosa may develop on the basis of many factors, but it is primarily associated with a psychic background.[1] It has been pointed out by Berkman[2] that there is a wide line of demarcation between undernourishment and anorexia. This point had been expressed previously by Gull[3] when he considered that anorexia nervosa was a condition resulting from starvation. Voluntary or forced starvation in itself presents a picture similar to true anorexia nervosa, and extensive studies[4] have given no evidence of a primary metabolic disorder. Most patients fall into the younger age group, and those over 30 years of age comprise a small percentage of the whole. Furthermore, it has been shown[5] that the older the patient the more resistant he is to treatment, probably due to his fixed ideas and inability to coöperate.

Insofar as the treatment of this condition is concerned, it has been principally dietary,[6] and it has been assumed that a high caloric diet must be maintained for months before normal weight is approached. Prior to 1938, desiccated thyroid appears to have been a necessary part of all medical therapy.[5] Since that time, some observers have felt that thyroid should not be included[6] on the ground that the basal metabolic rate (which, as one would expect, is generally low) will show a prompt response toward the proper level; this precludes an initial gain in weight, a most important point from the psychologic aspect. The main stumbling block in most of these cases has been the associated vomiting; when this symptom has been paramount, positive treatment has been most difficult.

Generally speaking, the symptoms have been classified as psychic and somatic. The former include the emotional reactions of a spoiled child, unsound excesses, apathy, reticence, fatigue and negativistic tendencies. Among the latter are marked loss of weight, pallor without anemia, dryness of the hair and skin, low basal metabolic rate, intolerance to cold, amenorrhea, atrophic uterus, and similar changes consistent with starvation.

Successful control of anorexia by dietary therapy has not been the entire problem. The distressing symptoms concomitant with increasing the bulk of the diet have caused many cases to become refractory, even though the amount of

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food has been increased very gradually. More recently, Berkman has felt that proper regulation will rarely result in failures,[7] and those primarily in the older group. It has been stated further that cases of a psychotic (schizophrenic) or definite compulsive background do not respond in an encouraging manner.[8] In most instances, patients who have responded in a satisfactory manner to dietary therapy have indicated progress by a slow gain in weight over a period of a month. Nevertheless, it has been pointed out that occasionally, in spite of the effect of initial waterlogging, as much as 24 pounds have been gained in a single week[9] without evidence of gastrointestinal distress.

In the following case the patient was refractory to the usual methods of treatment; and this in addition to her age and the presence of psychotic traits led to the adoption of surgical measures.

Case Report

This 36 year old female was admitted to the Worcester City Hospital on April 22, 1948, with a history of intermittent loss of weight over a period of 20 years. There were times during this interval when the patient tended to gain some weight, but since the age of 15 her weight had never approached a normal level. The onset of her difficulty dated back to her second year in high school. At that time it had been noted that she was shy and had difficulty "being herself around boys." The first somatic indications were vomiting and amenorrhea. She felt that she didn't want to grow up and stated that during her course of life she had had but "about six periods." She manifested unhappiness about these periods because they were "dirty." Prior to the onset of the symptoms, the patient had experienced an abnormal home life. Her mother had died at the birth of a younger brother. This event was followed by the remarriage of her father to a woman the patient did not get along with or like. Although constantly underweight (in spite of periodic gain), the patient managed to finish high school and to enter nurses' training school. She stated that she had wished very much to finish her training but had been forced to give up after two years. Because of her persistent symptoms at that time, she had thought a rest would help her, but intended to return to complete her course when she had gained sufficient weight. However, this never happened; her weight loss continued and the anorexia increased in severity.

In 1936 she entered a State institution on a voluntary basis, where she remained for one year. At that time her condition was unchanged, and her summary of the hospitalization was, "If you don't bother anyone, they don't bother you." Subsequently, she engaged in many different jobs: housemaid, clerk, factory worker and cook, all terminating after short intervals due principally to her fatigue. Over the years her social contact gradually narrowed to a single person—"a girl friend"—whom she had met as a patient at the State Hospital. All contacts with other friends had dwindled gradually and she had never had any desire for male companionship. Similarly, contact with her own family had lessened chiefly because she felt that "they ought to be ashamed of me—the way I look." The two years prior to this admission were characterized by a continued loss of weight without periods of remission. Any semblance of appetite had practically disappeared and she took but small amounts of solid food. She stated that solid food and eggnogs and milk always made her vomit.

Finally, the patient reached the decision to seek a "psychoanalysis in Boston," but thought that as an initial approach she would enter the Worcester City Hospital for a check-up. She stated that she was well aware of a mental conflict but knew that she did not have a "psychosis."

Physical Examination: On admission, physical examination revealed an emaciated, pale appearing 36 year old woman. Although showing evidence of fatigue, she was in no acute distress. Her weight was 55 pounds; her temperature, 97.4° F.; her pulse, 76. Her skin was noted to be rough and scaly, and the extremities were cold and cyanotic. Otherwise, except for the findings of extreme emaciation, the physical examination was not remarkable.

During the examination, the patient exhibited emotional instability and cried frequently. She talked incessantly and freely, making such statements as, "When you stop eating, you lose weight and then you don't want to eat because you might gain. If you were to tell me I was looking better, I would worry and start to feel

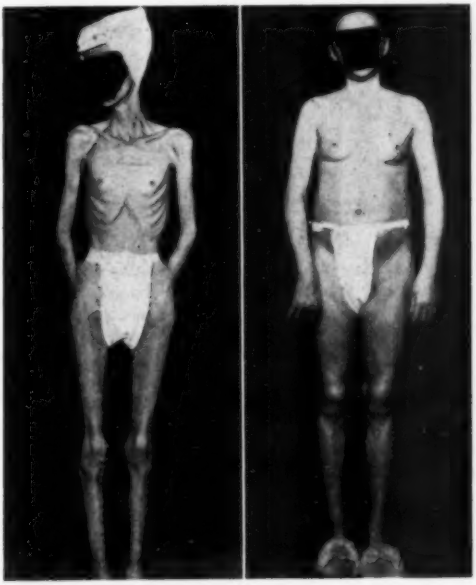

FIG. 1. (*Left.*) This photograph, taken before operation on June 7, 1948, shows the general appearance of the patient; her weight was 54 pounds.

FIG. 2. (*Right.*) This photograph shows the appearance of the patient three months following operation; her weight was 142.5 pounds.

bad and worry because I wouldn't know why I looked better. If you told me I looked worse, it wouldn't bother me at all. I don't want to die, I haven't lived yet. Nobody can help you unless you help yourself. I wanted to gain weight, but, then I didn't want to. I don't have a psychosis."

Laboratory data showed a basal metabolic rate of minus 35 and a hemoglobin of 84. All other tests, including extensive roentgen-ray examination, were within the normal levels.

The hospital course was marked by an attempt to regulate the patient with respect to a dietary régime. The situation was discussed with her at length, especially concerning the importance of increasing her caloric intake. During these inter-

views, the patient always expressed her desire to coöperate and to gain weight. A 1,300-calorie diet was thought to have been attained but persistent reports by the nurses soon indicated that the patient, immediately after eating, would gag herself and vomit. The patient's weight chart varied but little during the next six weeks. On April 22, 1948, her weight was 55 pounds; on April 24, 52 pounds; on June 6, 54 pounds. The diagnosis of anorexia nervosa with obsessive-compulsive characteristics was made. It appeared that the problem was an intractable one and, when the medical, psychiatric, and neurosurgical services had considered all the data, it was felt that a prefrontal lobotomy offered the only hope for improvement. This decision was discussed with the patient in considerable detail and she consented, but with the statement, "Although I feel that I want to get well, maybe, within me, I don't want to get well."

Accordingly, on June 7, 1948, a bilateral lower quadrantic prefrontal lobotomy was performed. The postoperative course was marked by some mental confusion, which largely cleared over a period of 10 days. On the first postoperative day it was noted that the patient was eating and drinking well. She was allowed out of bed on the second postoperative day. The increase in weight from that point on was remarkable. On June 13, 1948, six days following surgery, her weight was 63 pounds, a gain of 9 pounds. By July 1, about three weeks from the date of operation, her weight had risen to 84 pounds. During this period the patient went through the various phases seen in many postoperative lobotomy cases, but to a lesser degree. Lack of inhibition probably best characterizes her behavior; as an example, her language frequently gave way to a choice of words she formerly shunned; also, she took considerable delight in drawing obscene pictures on the nurses' desks. These traits subsided, and in their stead definite constructive initiative appeared, and the patient began to do some chores about the ward. Nevertheless, she failed to do this work in an adequate manner. If the job happened to be a long one, she would tire or lose interest rapidly. As time went on, it was noted that she showed increasing interest in being occupied. She finally insisted that she was ready to be discharged. Ordinarily, she would have been discharged at a much earlier date, but because she had no one to look after her during her convalescence and because of the extreme interest of the staff, she was not discharged until September 10, 1948, approximately three months following the prefrontal lobotomy. Questioned at the time of discharge concerning her ability to earn her living, the patient said she was certain she could do housework or practical nursing. Her weight at that time was 142.5 pounds.

For the next eight months, her course was marked by a succession of jobs, the longest lasting about four months. As the patient put it, "Always hired and always fired." Her main problem was not associated with any inability or lack of desire to work but was due primarily to her being unable to refrain from excesses. As an example, one employment was terminated because she smoked too much—six to eight packages of cigarettes daily. She accomplished her tasks satisfactorily but it was felt that her constant smoking would "set the house on fire." Also, she was overcritical of people, to the extent that her employers had difficulty in getting along with her.

During this period, from September, 1948, to May, 1949, her weight remained fairly stable, averaging 145 pounds. In December, 1948, six months postoperatively, she menstruated for the first time in many years and accepted the event without revulsion. She saw her family occasionally without the sense of being "ashamed." The tendency to excesses and the inability to get along with people—even though improvement in these respects had been noted—demanded a period of further convalescence under institutional care, especially since her home situation prevented her remaining there.

Accordingly, she was admitted to an institution, on a voluntary basis but under routine and discipline, where she worked for her maintenance. When she first arrived, it was thought that she would have to leave because of her extremely critical attitude and her feeling of superiority to her associates; she became a greater problem than she had been while working in private homes. The next several months were characterized by gradual but definite improvement in these respects. She did her work more efficiently and began to show a decided interest in sewing.

Her last follow-up, March 19, 1950, revealed the patient's physical condition to be excellent. At that time she weighed 150 pounds. There had been no indication of any return of nausea and, on specific questioning, the patient stated that she had not vomited since the operation. She also stated that she had begun to realize during the past few months what her main faults had been. She was fully aware of having been over-critical and she also realized that she had been "bold." She further stated that at the time of discharge from the hospital she had thought she could hold a job without difficulty. Now, she realized that she had been completely incapable of doing so. At the interview, her one concern revolved about a feeling of guilt. When questioned concerning this guilt, she explained that she was afraid she had harmed herself physically for so many years, she didn't see how it was possible she could feel so well at the present time. She had gained much insight. She appeared emotionally stable and volunteered that she was a "new person" and was happy that the operation had been performed. Her father voices the same feeling without reservation. It was the opinion of her supervisor that the patient's work, her personality, and her ability to get along with her fellow-workers had now approached a normal level, and that she could hold an independent job without difficulty.*

Comment

This case represents an unusual problem from the point of view of treatment. Medical and psychiatric therapy had failed and it was only as a last resort that prefrontal lobotomy was undertaken. The lower quadrantic procedure was carried out with the point in mind that her mental status would be less affected and, therefore, her convalescence would be shortened. The latter might have been the case if the patient had been able to return to her home. Attempting full-time employment three months postoperatively required too great a readjustment and, we believe, reacted in a deterring fashion. Then again, it is not certain that sectioning only the lower quadrant is less drastic in effect than a complete prefrontal procedure. Although the initial impact appeared to be less severe than in most lobotomized patients, the subsequent period of recovery extended over as long an interval as many complete procedures have required. Postoperatively, the patient exhibited the frequent tendency of many lobotomy cases, namely, an increase in appetite and weight. Also, it was noted that, with the rapid increase in weight, there was no objective evidence of the water logging which has tended to take place in many patients recovering from anorexia nervosa. Another point must be mentioned: prefrontal lobotomy is not recommended as the treatment of choice in all cases of anorexia nervosa. Certainly the majority, as Berkman has shown, will recover by proper medical means. We feel that it should be considered only in the refractory cases who have failed to show any evidence of response and in those patients who are frankly psychotic or who are manifestly of the obsessive-compulsive group.

* Since July 1951, this patient has supported herself completely.

Conclusions

A refractory case of anorexia nervosa with obsessive-compulsive characteristics treated by prefrontal lobotomy has been presented.

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GARGOYLISM (DYSOSTOSIS MULTIPLEX): TWO ADULT CASES WITH ONE AUTOPSY *

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Gargoylism is a heritable and congenital condition, attributable at least in part to defects in cartilaginous development which lead to dwarfism and to numerous characteristic deformities of the skeleton. The osseous abnormalities were first described by Hunter [1] in 1917. Two years later Hurler [2] reported cases with similar deformities and with cloudiness of the corneae and mental deficiency. Husler,[3] who is responsible for the name "dysostosis multiplex," included the condition described by Hurler in his group of degenerative dysostoses. English writers coined the term "gargoylism." [4, 5, 6, 7, 8] There is some confusion in the literature in both designation and description: isolated cases have been incorrectly included in series of other similar, possibly related diseases. Hurler described her cases as multiple degenerations of the skeletal system and called them osteodysplasias. Others have recorded cases under such titles as scaphocephaly,[9, 10] acrocephaly,[11] chondrodystrophy with infantile myxedema [12] and Morquio's disease.[13] Washington,[14] impressed by the finding in some of the autopsied cases of a substance in the cells of the brain and other organs which he thought was lipid in nature, suggested that the condition may be related to lipoid

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histiocytosis and should be called lipochondrodystrophy. Lindsay and co-authors [23] have histologic and histochemical evidence that the malady involves abnormal storage of a macromolecular substance such as glycogen or a glycoprotein.

In the previous literature there are records of well over 100 patients, 24 of whom were autopsied.[15, 16, 17, 18, 14, 19, 20, 21, 22, 23, 24] Among these are certain cases [25, 18, 22] which are not entirely characteristic.

Certain clinical features tend to be more or less constant. Among these are dwarfism, a marked shortening of the trunk and neck, an enlarged and misshapen skull, low placed ears and a face with prominent forehead, protuberant temporal bones and short nose with depressed bridge and broad base. In many of the cases there appears to have been an early closure of all cranial sutures except the coronal. In some, a keel-like ridge has marked the hyperostosis and early closure of sagittal and metopic sutures. In several cases a marked elongation and anterior "pocketing" of the sella turcica have been observable in roentgenograms of the skull. The hands have been large, with marked limitation of the extension of the fingers. In some there has been a bilateral radial deviation of the little fingers. Difficulty in extension has been a prominent feature, most notable in the shoulder and elbow joints but also tending to affect the knees and hips. Supination and pronation are also greatly limited. Talipes equinus has been common. In all cases the abdomen has been prominent, with pouting, low-hung umbilicus and not infrequently with umbilical hernia. Kyphosis of the lower dorsal and lumbar vertebrae or of the lumbar region alone has often been noted. In most instances the liver and spleen have been found well below the costal margin. Haziness or cloudiness of the cornea is present in about 75 per cent of cases. Deafness, sometimes almost complete, is frequent. Mental deficiency has been much emphasized but is an inconstant feature. Peculiar granules in the neutrophilic leukocytes have been observed.[27] The hereditary nature of the malady has been fairly well established and has been attributed to the transmission of a single recessive autosomal gene.[28]

Nearly all reported cases of this disease have been in babies and children. Therefore, our two cases are of special interest in that they were adults: one a 28 year old man who came to autopsy after 22 years' observation, the second a man still living and reasonably well at age 29.

Case Reports

Case 1. The first patient, observed over a period of 22 years, presented several extraordinary features.

The patient was referred to T. C. H. on June 6, 1918, by Dr. George Hourn. He was then five and one-half years of age. His mother stated that he had been born at full term, and that the delivery had been difficult and had been completed only with the aid of instruments. The boy walked well at the age of 11 months and began to talk at the end of the first year. His parents considered him mentally normal. He had frequent upper respiratory infections, with a rather persistent bronchitis, but none of the more serious diseases of childhood.

Examination in the St. Louis Children's Hospital revealed a boy of extraordinary appearance (figure 1A). His thick, heavy eyelids and large tongue, partially protruding between thick lips, gave him a cretinoid appearance, but he was obviously not a cretin. He was playful, happy and mentally normal. There was no bradycardia. He was not constipated and he perspired normally. His height was 91 cm.

(36 inches). His enlarged head had a maximal circumference of 52 cm. (20.5 inches). It was markedly dolichocephalic and was broadest in the occipital region. There was bulging of the parietal regions and of the forehead. The suture lines could be felt as ridges. The nose was short and broad with a marked depression

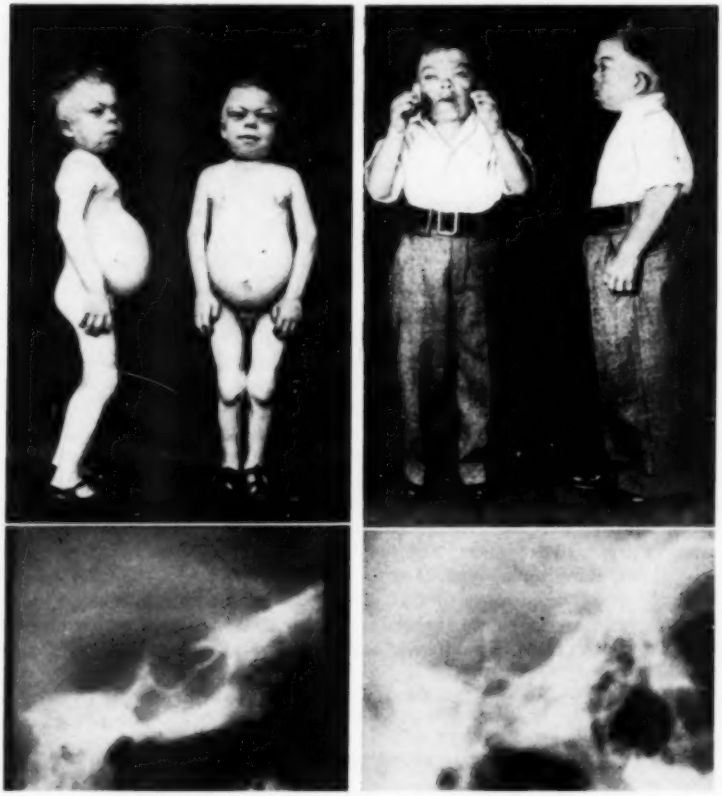


FIG. 1*A*. (Upper left.) Case 1, Charles B. at the age of five and one-half years. Low placed ears, flexed ears, flexed hands, knees that cannot be fully extended. Protuberant abdomen and umbilical hernia. *B*. (Lower left.) X-ray of the sella turcica at five and one-half years. Note the striking elongation and anterior "pocketing" of pituitary fossa and the slight increase in depth.

FIG. 2*A*. (Upper right.) Photographs of the patient at age 19. *B*. (Lower right.) X-ray of the sella turcica showing the progressive increase in size.

at the root, which was accentuated by the prominence of the frontal region. The hair was coarse and sparse. There were ocular hypertelorism and proptosis, but a large portion of the eyeballs was covered by the thickened lids. No corneal opacity was noted on this or on subsequent examinations. The ears were set low on the head. Otoscopic examination at this time revealed no abnormality. The tonsils were large.

red and cryptic. The neck was short. Breath sounds were harsh, with showers of moist râles and wheezing at the end of inspiration. The abdomen was protuberant, with a large umbilical hernia. The liver extended to the umbilicus and the spleen was thought to be grossly enlarged. The elbow and knee joints and the knobby joints of the large hands could not be fully extended. There was a slight genu valgum. At this time there was no hematologic abnormality. Roentgenograms of the hands showed no evidence of delayed ossification in either carpus. Roentgenogram of the skull showed a distorted appearance of the sella turcica (figure 1B), which gave rise to discussion of a possible pituitary tumor.

The umbilical hernia was repaired, and after an uneventful postoperative course the patient was discharged.

During the winter of 1918–1919 he had on several occasions a discharge from his left ear, in which he had become deaf. Otherwise his health had been good. The bronchitis had become less troublesome. His hair had become softer in texture and more abundant. The ear drums were examined by Dr. Hourn, who considered them normal. At this time the red blood cell count was still normal. A fragility test showed hemolysis beginning in 0.44 per cent salt solution and complete in 0.34 per cent. The tonsils and adenoids were removed.

During the spring of 1919 the boy began to suffer from occasional nose bleeds which at first caused no anxiety. By April, 1922, however, they had become severe and frequent, lasting from two to three hours and requiring packing of the nose. Often they were followed by severe epigastric pain, relieved by the vomiting of thick, black blood. He became progressively weaker and was re-admitted to the St. Louis Children's Hospital on July 11, 1922. Examination revealed marked pallor, puffiness of the eyelids and edema of the ankles. Breathing was difficult and stertorous. There were palpable lymph nodes in the neck, axilla and inguinal regions. The liver and spleen were still enormous. The red blood cell count was 1,750,000, with marked anisocytosis and poikilocytosis. The white blood cell count was 3,700, with a normal differential. The coagulation time was 20 minutes. The prothrombin time according to Howell's method was considered normal. In tests for osmotic fragility of the red blood cells hemolysis began in 0.61 per cent sodium chloride solution and was complete in a 0.38 per cent solution. The blood clot did not retract normally, although the platelet count was normal. Some confusion arose concerning those tests because they were not done simultaneously. The red blood cell count was taken before the boy received a transfusion from his father, whereas the other tests were made later. Later examinations by Dr. Alexis Hartmann revealed a coagulation time of 40 minutes, without lengthening of prothrombin time and with normal fragility of red blood cells.

On July 13, 1922, a splenectomy was performed by Dr. Evarts Graham. Anesthesia was difficult, and frequent artificial aid to the respiration was necessary. The liver was enlarged but without any gross evidence of cirrhosis, and a biopsy revealed numerous mononuclear cells in the perivascular spaces. The spleen weighed 245 gm. and measured 14 by 8.5 by 4 cm. On cut section it was described as beefy, with fine, small, whitish nodules which projected above the surface. Microscopically it revealed enlarged sinusoids and a slight fibrosis.

Following splenectomy, the white blood cell count increased to 34,900 and gradually fell during two months to 12,000, the red blood cell count rose to 4,000,000, the hemoglobin to 75 per cent. In October, 1922, his red blood cell count was 5,000,000; hemoglobin, 75 per cent; white blood cell count, 11,000. The coagulation time was only 14 minutes. Hemolysis began at a 0.45 per cent salt solution and was complete at 0.25 per cent.

No further hemorrhage was noted until May, 1923, when the patient suffered from frequent epistaxis with consequent anemia. At this time his red blood cell

count was 2,400,000, the white blood cells numbered 14,000, the coagulation time was 8 minutes. Bleeding stopped immediately after entrance to the hospital and did not recur.

The boy was not seen again until July, 1932, when he was brought to Barnes Hospital for reëxamination. During the interval he had had no hemorrhage and no symptom suggestive of a severe anemia. His appearance at this time is shown in

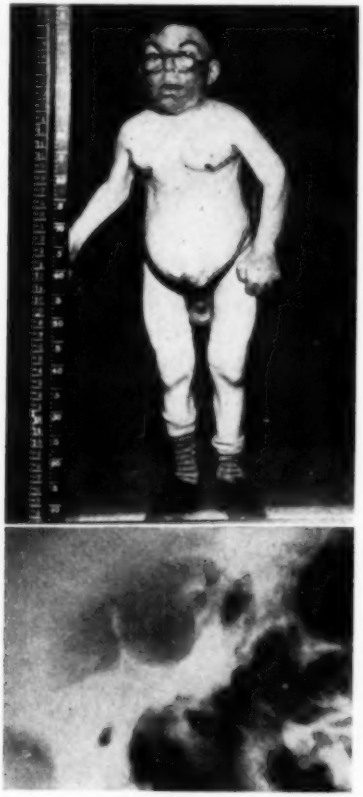


FIG. 3*A*. Photograph of Case 1 at age 25. *B*. Further enlargement of the sella turcica demonstrated at age 25.

figure 2A. He weighed 58 pounds and measured 45.5 inches, having gained 11 pounds and grown five inches in a period of approximately 10 years. His hands had grown out of proportion to the rest of his body and presented a claw-like appearance. There was increased difficulty in extension and rotation at the hips and shoulders and limited extension at the elbows, with limited pronation and supination of the forearm. The deafness had greatly increased. His blood presented no ab-

normality. He was uncoöperative, moody and subject to fits of anger. Attempts to estimate his intelligence were defeated by his unwillingness to be examined, his deafness and his distrust of physicians.

Examination of his hearing by Dr. L. W. Dean and Dr. C. C. Bunch showed a marked bilateral diminution in bone conduction. He could hear only the loudest tones. Dr. Dean considered that he had a deafness of the inner ear type.

Examination of his eyes by Dr. W. M. James showed vision of 6/12 on each side. The fundi were clear and the visual fields within normal limits. The defect in vision was attributed to a high degree of compound hyperopic astigmatism.

Roentgenograms of the skull showed an increase in the enlargement of the sella turcica (figure 2B).

In March, 1938, the boy was admitted to Barnes Hospital complaining of severe frontal headaches and of frequent nosebleeds. His breathing was difficult and stertorous. The breath sounds were almost obscured by sibilant and sonorous râles. The blood pressure was 110/75 mm. of Hg, and the heart was not considered abnormal. The liver extended 15 cm. below the right costal margin (figure 3) in the midclavicular line. The deformity of joints appeared to be more marked. The elbows could be extended to approximately 130°, and the patient believed that his hands were stiffer than formerly. He was more coöperative and could read ordinary newspaper print well with the aid of glasses. Except for the auditory defect, the cranial nerves were normal. Further enlargement of the pituitary fossa was demonstrated in roentgenograms of the skull (figure 3B). Nasal packs stopped the bleeding. Blood studies before and after the bleeding were normal except for a low red blood cell count.

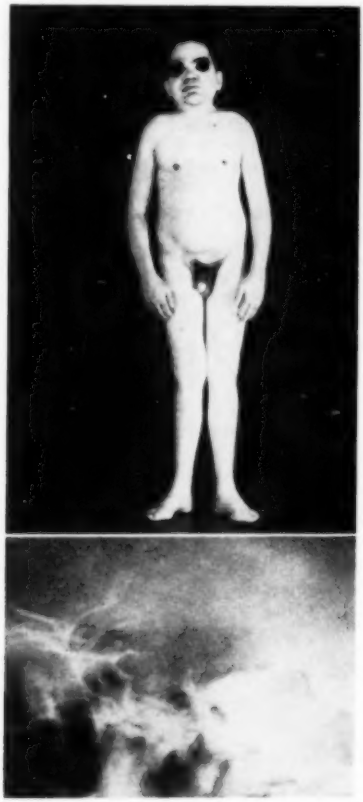
On July 15, 1940, he was seen because of urgent dyspnea, severe cyanosis, orthopnea, venous engorgement and marked distention of the abdomen. He returned home but became worse. It appeared that death was due to suffocation. His supply of air, always precariously low because of his deformities and his chronic bronchitis, may have become totally insufficient with the upward pressure exerted by increasingly distended bowels in an already distended abdomen.

Family History: A maternal great-uncle had a head shaped like that of the patient. He was dwarfed and had an abnormally protuberant abdomen. An uncle, the mother's brother, greatly resembled the great-uncle. He was 4 feet tall and also had abdominal and cephalic deformities. He died at the age of 27 of dropsy and asthma after an illness of seven years. Both the great-uncle and uncle were considered unusually bright by the family. A first cousin on the mother's side was considered by the family to have a head and abdomen shaped like the patient's. This boy died at the age of 14 within 24 hours of the onset of sudden pain in the head and convulsions. He was intelligent, had grown normally to the age of 14 and was considered well until the time of the fatal illness. None of these relatives was deaf. It is not evident that any one of them had stiffness of joints, although both the uncle and cousin were said to have had hands large for their size and resembling even during childhood the hands of old men. The patient's sister developed normally.

Roentgenologic Studies: The roentgenograms require special discussion. Roentgenograms of the skull were taken at different ages. In the earliest, taken when the boy was five and one-half years of age, it was noted that both the lambdoid and sagittal sutures were closed and that the coronal suture was open and prominent. The anterior fontanel was not closed. The sella turcica was elongated (figure 1B). The mastoid processes were low. The temporal bones were unusually prominent and bulged out from a somewhat narrow vertex. The frontal region was prominent. The diploic veins were prominent.

Later roentgenograms of the skull, taken at the ages of nine and one-half and 19 years, revealed gradual closure of the coronal suture, tremendous diploic blood

vascular spaces in the frontal bone and arterial grooves throughout the remainder of the calvaria. The pituitary fossa showed a progressive enlargement and elongation in the anteroposterior diameter, with some increase in depth (figure 2B). Although the dorsum sellae was thin in its anteroposterior dimension, no erosion or destruction of bone was evident. The distinctive shape should be noted. In all of the pictures there appeared to be a pocket or space in front of the sella itself and below the



A

B

FIG. 4*A*. Case *2*, Leonard G., in fair health at age *29*. *B*. X-ray of the sella turcica of case *2* to demonstrate the characteristic elongation with anterior "pocketing" and some increase in depth of the pituitary fossa.

anterior clinoid processes, which seemed to be placed far anterior to their usual position (figures 1B, 2B and 3B). It was noted in an x-ray of the hands at the age of 10 that there was little evidence of delay in ossification of the bones of the carpus. The metacarpal bones were seen to be thickened, widened, bowed and of irregular contour. Even at the age of 19 the epiphyses were not united. The line of ossification was irregular in the diaphysoepiphyseal junctions, this feature being particularly evi-

dent at the lower ends of the radius and ulna. There was irregularity of the articular aspects of all of the epiphyses. In the metacarpophalangeal joints a tendency to increased thickness on the radial side of the epiphyses was evident. The increasing limitation of extension was apparent, but its cause, possibly associated with the irregular and uneven ossification, was not altogether apparent from inspection of the roentgenograms.

A bilateral bowing indicating an increase in the length of the radius was noted. The hip joints visualized at the age of five and one-half years showed no striking abnormality. The ankle joint at 19 years showed epiphyseal cartilages still present, but no evidence of bone change comparable to that in the forearm.

Necropsy Findings: The examination was performed nine hours after death. The body weighed 25 kg. (55 pounds) and was 119 cm. (47 inches) in length. The appearance of the face and body corresponded to that portrayed in figure 3A. The head was elongated, and there was a moderately conspicuous ridge in the region of the metopic suture. Extension of the elbows, fingers and knees was greatly limited. The abdomen was tremendously distended and the wall was thin. Just to the left of the midline was a healed scar measuring 15 cm. in length.

The thymus weighed 7 gm. It was pinkish-gray, soft and coarsely lobulated. Microscopically the separation of the cortex from the medulla in individual lobules was indistinct, there being equal numbers of lymphocytes in the two parts. Hassall's corpuscles were large and well keratinized. About the lobules were a moderate number of eosinophilic myelocytes. This picture was considered one of moderate involution of the thymus, somewhat delayed for age 28 (Boyd). The thyroid gland weighed 25 gm. and was composed of small and moderate sized acini, lined by vacuolated pale cells and containing scant colloid.

The heart weighed 260 gm. The circumferences of the valvular rings were within normal limits. The margins of the tricuspid and mitral valvular cusps showed slight fibrous thickening, and each presented several distinct hemispheric aneurysms, varying from 2 to 5 mm. in diameter.

In one large bronchus there were slight thickening and hyalinization of the basement membrane and slight lymphocytic infiltration of the submucosa. There was no infiltration with eosinophils, no hypersecretion of mucus, or other evidence of asthma. The examination failed to reveal an anatomic basis for the difficult breathing from which the patient had so frequently suffered. The intestines were enormously distended with gas.

The liver weighed 1,680 gm. The general contour was normal, but the inferior margin was rounded and extended 8 to 10 cm. below the costal margin in the right midclavicular line. The external surface was firm, smooth, shiny and dark yellowish-red. Microscopically the hepatic cells were large, sharply outlined and variable in shape. In the cytoplasm were droplets of finely granular glycogen (Best's carmine stain). Scharlach R stain failed to stain the droplets.

The 245 gm. spleen had been removed surgically at the age of nine and one-half years. Review of the sections revealed no striking abnormality. The general architecture was intact and the lymphoid follicles appeared to be normal. The combined weight of the adrenal glands was 20 gm. They were grossly normal, but a few cells of the medulla were enlarged and vacuolated.

The prostate gland was slightly smaller than that of the average adult. The testes weighed 40 gm. together and showed no gross changes. Microscopically, rare, mature spermatozoa were present. Most of the cells in the tubules had developed only to the stage of spermatids.

The lymph nodes throughout the body were small, soft and discrete. Microscopically, the germinal centers were few and small and the nodes were less cellular than usual.

The bone marrow exhibited increased cellularity due to the presence of reticuloendothelial cells, a few of which were vacuolated.

The bones of the calvaria were harder than normal but of normal thickness. The squamous portion of the temporal bone was enlarged and prominent externally, whereas the petrous portion was unusually small in all diameters. The sella turcica measured 12 mm. in depth and was about twice normal size. The pituitary gland showed no abnormality except for a few vacuolated, unidentified cells in the anterior lobe and several vacuolated cells in the wall of the infundibulum.

The brain weighed 1,500 gm. Except for a few small cystic spaces of healed encephalomalacia in the central portion of the basal ganglia, no pathologic change was found either grossly or microscopically.

Examination of the right elbow joint showed limitation of extension beyond about 130°. Sagittal section showed that the lower end of the humerus curved to present the articular surface ventrally instead of caudally. The curve was of such extent as to limit extension by about 60°. The joint surfaces and other structures were intact grossly.

Ears and Temporal Bones: Detailed studies by Dr. Dorothy Wolff,[20] of the Department of Otolaryngology, revealed the following: There was partial atresia of both external auditory canals. The mastoid antrum was smaller than normal in both ears. There were almost no parantral cells and relatively few bony trabeculae. The lacunae for the most part were devoid of cells, giving to the bone a necrotic appearance. No joint cavity was visible in either malleoincudal joint. Shrapnell's membrane was not fully formed, and Prussak's pouch was smaller than normal. The inner ear showed an irregular contour of the semicircular canals. In the cochlea, Reissner's membrane was intact throughout. The spiral ligament showed numerous cystic spaces. There was degeneration of the stria vascularis. The organ of Corti preserved its normal contour, but no cellular structure could be identified. Rosenthal's canal was either devoid of nerve fibers or contained only a few hollow strands of neurilemmal sheath. The spiral ganglion cells were not appreciably decreased in number but stained very faintly and revealed vacuolated cytoplasm.

The following were essentially normal upon gross and microscopic examination: parathyroid bodies, lungs, gall-bladder, bile ducts, pancreas, urinary system and gastrointestinal tract.

Comment

This case had the general characteristics of dysostosis multiplex, although certain features were lacking. Corneal opacities and mental deficiency were not present. Appraisal by the Yerkes-Bridges test at St. Louis Children's Hospital by Dr. G. B. Smith when the patient was nine and one-half years old showed a mental age of the eight year level, although the patient was handicapped by his deafness. Subsequently, his tendency toward introversion made further evaluation difficult. However, none of the clinical and autopsy findings indicated any mental defect in the case. This is in contrast to some cases, which showed ballooning of cerebral ganglion cells by an abnormal substance.[15, 17, 22-24]

The deafness was shown clinically to be of the inner ear type. Pathologically there was vacuolation of cells of the spiral ganglion to explain the deafness. However, the ankylosis of the malleoincudal joint could be used as evidence that initially the auditory defect was of the conduction system and that the inner ear changes were merely secondary. *The bleeding* may have been due to coagulation defects, possibly thrombocytopenia secondary to the enlarged spleen, although this

cannot be proved. A local bleeding point of the nose was undoubtedly an important factor, because no other site of hemorrhage was demonstrated. Bleeding is not a common feature in gargoylism.

Hepatomegaly and splenomegaly have been emphasized in most of the recorded cases of dysostosis multiplex, with the notable exception of two necropsied cases of Ashby, Stewart and Watkin.[17] Our patient had an enlarged liver at death (1,680 gm. in a dwarfed individual), and had been relieved of a 245 gm. spleen at the age of nine and one-half years. The absence of lipoid-like material in the liver observed by others [18] and the presence of glycogen of similar appearance may be worthy of note, especially in the light of the studies of Lindsay et al.[23] These authors suggest that the hepatic changes are due to the abnormal storage of a macromolecular substance, perhaps glycogen or a glycoprotein.

Mode of death of many of the cases has indicated a peculiar tendency to unexpected and rapid exitus. This has been frequently interpreted as sudden cardiac failure, circulatory collapse, pulmonary edema or "bronchopneumonia." Our patient died suddenly during a period of increasing, finally intolerable dyspnea which previously had simulated asthma. Pathologic examination failed to show evidence of asthma or to present a good explanation of the final phase of his illness. The nodular thickenings and small aneurysmal formations on the margin of the leaflets of the mitral valve, while of interest, were not sufficient to cause death. Similar findings have been repeatedly recorded and may well be an inconstant characteristic of the disease.

Endocrine Glands. No constant change has been demonstrated in the endocrine organs, although involvement of certain endocrine tissues is common. In one case [18] the pituitary gland was enlarged owing to infiltration of all types of individual cells by a "lipid-like substance." Infiltration of the chromophobe cells of the pituitary was observed in de Lange's [19] case. Ashby, Stewart and Watkin [17] noted enlargement of the pituitary gland in one autopsied case, and hyperplasia in another. Among the eight autopsied cases of Lindsay et al.[23] there was gross enlargement of the pituitary in one case, whereas six of the eight cases displayed microscopic alteration of the cells of the anterior lobe, particularly of the chromophobic cells. The altered cells were enlarged and indistinctly outlined and had a cytoplasm which was almost entirely clear. Some cells had bubbly, vesicular cytoplasm. The changes have been regarded as further evidence of an abnormal storage phenomenon. Changes are found inconstantly in other endocrine organs, notably the testis.[23] Other sites include thymus, thyroid gland and medulla of the adrenal gland. The thymus of Reilly's [16] 10 year old boy weighed 65 gm. Case 1 in Lindsay's series of eight autopsies, a 10 year old boy, had a 65 gm. thymus. One other of his cases (case 6) showed vacuolation of large mononuclear cells in the thymus. Our 28 year old man presented a 7 gm. thymus. The thyroid gland in our case was moderately involved microscopically, and there was relatively mild involvement of the pituitary gland, infundibulum of the pituitary gland, medulla of adrenal glands and bone marrow.

The liver displayed advanced infiltration of the cells. No active involvement of bones was demonstrated in our patient, probably because he was an adult.

The importance of enlargement and/or infiltration of endocrine and other organs is yet to be established. In the opinion of Lindsay et al.,[23] the infiltration interferes with function. Whether the alterations of growth are dependent mainly

on endocrine dysfunction or more directly on genetic influence is a matter of conjecture. Again, Lindsay has pointed to infiltration of a local site, the epiphysis, to explain the skeletal abnormalities. In the light of our confirmatory findings, we are inclined to agree with Lindsay and co-authors that (a) the commonly encountered endocrine involvement is one factor in the development of skeletal abnormalities, and (b) the infiltration of the epiphysis of a bone may retard its growth and alter its shape. However, the hereditary influence on bony growth may well predispose the patient to the characteristic skeletal pattern of gargoylism before the abnormal storage occurs.

The unusual ages of our 28 year old autopsied patient and our 29 year old clinical case (which follows) may well be due to the relatively mild involvement of vital tissues. We agree with Jervis [24] that mild forms occur, and we would like to suggest that systematic check through institutions might well yield a surprising number of borderline or mild cases in juvenile and adult persons.

Nature and Pattern of Skeletal Abnormalities. The pattern of abnormalities is perhaps best explained by considering the time of closure of sutures of the skull and of the epiphyses. According to Todd,[32, 33] the sutures of the skull normally commence closure soon after the twenty-first birthday. The sagittal suture is first to fuse, and the coronal and lambdoid sutures follow. The epiphyses of the long bones should be in the process of union between the fifteenth and twentieth years of life. Our personal observations (S. M.) have not confirmed the immediately preceding findings.

In our case, the closure of the sagittal and lambdoid sutures occurred before the age of five and one-half years. On the other hand, the epiphysis of the lower end of the humerus did not show complete union until after the twenty-fifth year. It is interesting to note that the early fusion of the sagittal and lambdoid sutures resulted in the usual dolichocephaly. Subsequent growth was in the anterior and lateral parts of the skull, with backward rotation of the posterior part. Therefore, the forehead and temples were prominent and the ears were low set. The growth of the anterior parts of the skull also resulted in ocular hypertelorism and in enlargement of the sella turcica.

Of the previously reported cases studied, it is noted that virtually all had an enlarged head, which of course occurs in rickets but not to the same degree. The constancy of an enlarged, deformed head, with associated typical facies, is interesting in the light of the work of Stockard.[31] By using many generations of several pure breeds of dogs, he was able to show that, with rare exceptions, the resulting cranial types did not arise from the deformity of a single bone. Usually they followed a pattern which did not vary widely and which was more or less constantly associated with a definite pattern of changes in the other bones of the body. It might be possible to regard the changes of dysostosis multiplex as possessing a genetic unity so definite that one individual with the condition could pass as a sibling of any other. It is difficult to imagine a relationship between so definite a skeletal pattern and an abnormal storage phenomenon, but evidently there is one.

Deformity of the Sella Turcica. The curious deformity of the sella turcica has been observed in all cases of gargoylism and is virtually diagnostic (S. M.). It is of some interest that only one other similar malformation (our case 2) was noted by Dr. Sherwood Moore in his roentgen examination of the skull of 16,000 individuals (in round numbers) over a period of 33 years. The material included

all ages and was about equally divided between the sexes. It is significant that there was no female case of gargoylism among the 16,000 examinations. Approximately 32 per cent of these cases were in the first and second decades and were from the St. Louis Children's Hospital and its clinic. The skeleton of a female dwarf in the Department of Anatomy has a sella turcica almost identical in conformation with that of these two cases but lacks the other bone changes. The enlargement of the pituitary observed in Ashby's two cases [17] suggests the remote possibility that the bony deformity might have resulted from hypophyseal hypertrophy, which in our case and in others had regressed before autopsy was performed. The absence of erosion of the clinoid processes and of the floor of the sella, however, is evidence against the hypothesis. It seems more likely that the increase and the malformation are integral parts of the general dysostosis of the skull.

Deformity of Joints. In the reported cases, one of the most constant clinical features has been a limitation in the extension of the fingers, elbows, knees and other joints. In our patient, the elbow joint itself was entirely normal and the limitation of motion apparently resulted from a forward bowing of the humerus, and a consequent ventral displacement of the joint surface of the elbow. Roentgenograms of other long bones revealed similar bowing, the cause of which cannot be definitely assigned but which was regarded as an irregularity of ossification due to involvement of the epiphyseal lines during the period of growth. In the case of dyschondroplastic dwarfs, the bone and joint conditions closely resemble those of dysostosis multiplex, but they do not have the changes in the skull and particularly in the sella turcica. Our autopsied case was an adult and therefore did not show the macrophages at the line of growth as demonstrated by Lindsay.[23]

Case 2. A 29 year old white man, a patient of Dr. Edward H. Reinhard, entered Barnes Hospital on May 9, 1949, with complaints of dyspnea and associated spells of "weakness in the knees." The latter had recurred about once a week during the preceding year, usually after he had been sitting for some time mentally engrossed, as at a desk or in a theatre. *Physical examination* revealed a 126 pound, short man with large head which was elongated anteroposteriorly. The head presented features of gargoylism, including depression of the bridge of the nose, low set ears and thick lips. The teeth were widely spaced, and the alveolar processes and teeth projected outward. The tongue was large and flat. There was a divergent strabismus associated with a paralysis of the internal oblique muscle of the right eye. The patient had effective vision of only the left eye, although both retinae were within normal limits by retinoscopy. The corneae were clear grossly and by slit-lamp examination. There was slight deafness of the nerve type, greater on the right. His voice had a rasping quality, and excessive mucus was present constantly in the throat. By indirect laryngoscopy the epiglottis appeared edematous. The short neck and the excessive mucus caused failure of direct laryngoscopy. The lungs were clear except for the sounds resulting from mucus in the throat. There was a soft systolic murmur but otherwise the heart was normal. His blood pressure was 120/80 and at another time 124/100 mm. of Hg. The abdomen was protuberant, and there were scars of umbilical and bilateral inguinal herniorrhaphy (performed when the patient was six years old). The liver extended 14 cm. below the right costal margin, and the margin of the spleen was palpable 10 cm. below the left costal margin. Small shotty axillary nodes were palpable. Pubic hair was sparse. The external genitalia were normal except that one testicle was not palpated. Rectal examination was negative. Neurologic study was not revealing except for the slight bilateral deafness of the nerve type. Many dark raised nevi were scattered over the body. The patient pre-

sented an abnormal posture, due to his short neck and narrow shoulders and to limitation of extension of certain joints. He was unable to abduct his arm more than 90 degrees. The elbows would not extend beyond 100 degrees, and there was an increased "carrying angle" of both elbows. The hands were of the "claw type," owing to inability to extend the joints completely. The fingers were held in flexion at an angle of 30 degrees. Stiffness of the back increased the abnormal stance of the patient. The femora were rotated inward on the pelvis and on the tibiae. Both feet showed talipes equinovarus.

Laboratory data presented counts of 4.39 million red blood cells, 3,100 white blood cells and 386,000 platelets per cubic millimeters of blood. The white cells were eosinophils, 4 per cent; bands, 4 per cent; segmented neutrophils, 44 per cent; lymphocytes, 38 per cent; and monocytes, 10 per cent. The red blood cells included 3.8 per cent reticulocytes. The bleeding and clotting times were 4.5 and 3 minutes, respectively. A bone marrow examination performed because of the leukopenia showed a normally cellular marrow. Urinalysis revealed no abnormalities. The Kahn reaction for syphilis was negative. The non-protein nitrogen was 18 mg. per cent. A glucose tolerance test and an adrenalin tolerance test were negative. The blood cholesterol was 172 mg. per cent. The cephalin flocculation and thymol turbidity tests were normal. Serum total protein was 7.2 gm. per cent with 4.7 gm. albumin and 2.5 gm. globulin. Serum calcium and phosphorus were normal. The prothrombin level was 70 per cent of normal. Bromsulfalein excretion test for liver function showed 2 per cent retention after 35 minutes following a dose of 5 mg. of the dye per kilogram of body weight. Urobilinogen excretion in the urine was normal. An electrocardiogram was essentially normal. The basal metabolic rate on two occasions was minus 13 and minus 16 per cent. Intravenous pyelograms revealed a left hydronephrosis of mild degree. A liver biopsy was performed on May 17, 1949. Microscopic sections were not remarkable except for the enlargement of the cells and the "fluffy" appearance of their cytoplasm. Glycogen stains showed abundant glycogen, whereas frozen sections stained with Sudan III revealed no fatty change. Chemical studies of lipids revealed slightly low cholesterol content in both liver and blood, as indicated by the following results:

	Observed Values	Normal Values
Liver Lipids Study (May 17, 1949)		
Fatty acids (neutral fat)	115.9	
Fatty acids (phospholipid)	6.1	
Fatty acids (cholesterol)	2.0	
Fatty acids total (mEq./kg.)	124	(125–225)
Lipid phosphorus (mg.%)	106	(75–125)
Cholesterol total (mg.%)	179	(250–400)
Free (mg.%)	104	(200–250)
Esters (mg.%)	75	(75–150)
Ratio (Free: Total)	.58	(.6–.75)
Cholesterol to lipid phosphorus ratio	1.7	(3–4)
Blood Lipids (May 14, 1949)		
Fatty acids (neutral fat)	3.1	(1–5)
Fatty acids (phospholipid)	4.6	(4.8–6.6)
Fatty acids (cholesterol)	2.3	(2.2–4.4)
Fatty acids (total) (mEq./liter)	10.0	(9–16)
Lipid phosphorus (mg.%)	7.8	(8–11)
Cholesterol total (mg.%)	126.0	(160–230)
Free (mg.%)	37	(40–55)
Esters (mg.%)	89	(120–165)
Ratio (free total)	.36	(0.25–.30)
Cholesterol to lipid phosphorus ratio	16.2	(19–25)

A *past history* of good health was given by the patient, who had been graduated from Oklahoma Agricultural and Mechanical College after completion of major studies in economics and accounting. He remembered having no contagious disease or serious illness. He stated that he had never been interested in women.

His *family history* was irrelevant except that the patient had a cousin who looked like him and had the same bony deformities. The patient's mother was well at age 55. His father had died in an accident at age 40.

The hospital course included therapy directed locally to his respiratory difficulties and stimulants to relieve his drowsiness, which was evident during his hospital stay. The patient returned to his position as "engineering aide."

Comment

This 29 year old patient, still living and in fairly good health, is unusual because of the duration of his life, lack of corneal opacity and auditory defects, and absence of mental retardation. Otherwise, the patient presents classic clinical, roentgenologic and pathologic (liver biopsy) features of gargoylism. The lipid studies on the biopsy of the liver and on the blood are particularly significant because of the low or normal values in all fractions. The fat stain revealed no excess of fat in the liver, whereas the glycogen stain (Best's) indicated the presence of a normal or an increased amount of intracytoplasmic glycogen. These findings (and the microscopic findings in our case 1) corroborate those of Lindsay and others who believe the disease to be a dysmetabolism of a substance related to glycogen. The chemical analysis of the biopsy of the liver refutes the argument of those who have suggested that a lipid or "lipid-like" substance is concerned in the disease.

Summary

The clinical, roentgenologic and pathologic findings of two cases of gargoylism are presented. The patients are distinctly unusual because of their relatively advanced ages of 28 and 29 years, respectively. One patient came to autopsy after 22 years of observation. The other patient is still living and fairly well. In both cases the roentgenograms, especially of the skull, are diagnostic. Complete autopsy in one case and biopsy of the liver in the second failed to exhibit excessive lipid or fat in the tissues. Chemical analysis of the biopsy showed no increase in lipids. Glycogen stains on the livers revealed abundant glycogen.

Conclusions

1. The disease gargoylism should be regarded as compatible with survival to adulthood in some cases.

2. The disease presents diagnostic roentgenographic features, particularly in the skull.

3. The basic defect in this hereditary disease is probably concerned with dysmetabolism of glycogen or an associated macromolecular substance.

4. Histologic, histochemical and quantitative chemical evidence is presented that the disease does *not* principally involve lipids.

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PULMONARY ADENOMATOSIS *

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PRIMARY alveolar epithelial hyperplasia or pulmonary adenomatosis in the human is very rare. However, *jaagziekte*, a disease in sheep closely resembling pulmonary adenomatosis in man, is quite common in Iceland, South Africa, Saxony, England and Montana. Even though the diseases, both clinically and pathologically, are similar, no definite relationship between the two has been established.

Swan [14] advanced three criteria for the diagnosis of pulmonary adenomatosis: (1) alveolar cell proliferation, characterized by appearance of cuboidal or tall columnar mucus-producing cells; (2) the absence of an intrinsic tumor of the bronchial tree, and (3) the absence of an adenocarcinoma elsewhere in the body.

The first case of pulmonary adenomatosis in man was reported by Helly [7] in 1907 as a multiple, nodular, bilateral tumor of the lungs. In 1942, Geever and Neubuerger [6] in summarizing 24 cases of what they termed alveolar cell tumors, made no distinction between alveolar cell carcinoma and pulmonary adenomatosis. Swan [14] recently found in the literature 27 cases of pulmonary adenomatosis reported since 1941, to which he added nine new cases from the files of the Army Institute of Pathology. He screened approximately 900 cases of pulmonary neoplasms and found only nine cases which fulfilled his criteria for adenomatosis.

The occurrence of metastasis and of carcinomatous changes in the lesions without metastasis leads to much confusion and controversy in the proper classification of these lesions. Many have probably been classified as alveolar cell carcinomas and unusual bronchogenic carcinomas, while others have been placed in the group of primary diseases causing alveolar cell hyperplasia.

CASE REPORT

History: A 51 year old white male farmer was admitted to the University Hospital on February 12, 1949, with the complaint of a productive cough, shortness of

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breath and weight loss of five months' duration. He had been treated by one of us (E. J. C. H.) in July, 1942, at which time he complained of periumbilical pain of several years' duration, occasional bright red blood in his stools and weight loss of 13 pounds. A gastrointestinal series showed no significant abnormality. Because of tenderness about the terminal ileum, an exploratory laparotomy was performed. No abnormality was encountered and the appendix was removed. Roentgen examination of the chest at this time revealed a normal chest.

In 1943 the patient was again seen because of epigastric pain, which was present most of the time but partially relieved by the intake of food. Another gastrointestinal series showed a gastric ulcer on the lesser curvature. This did not respond to

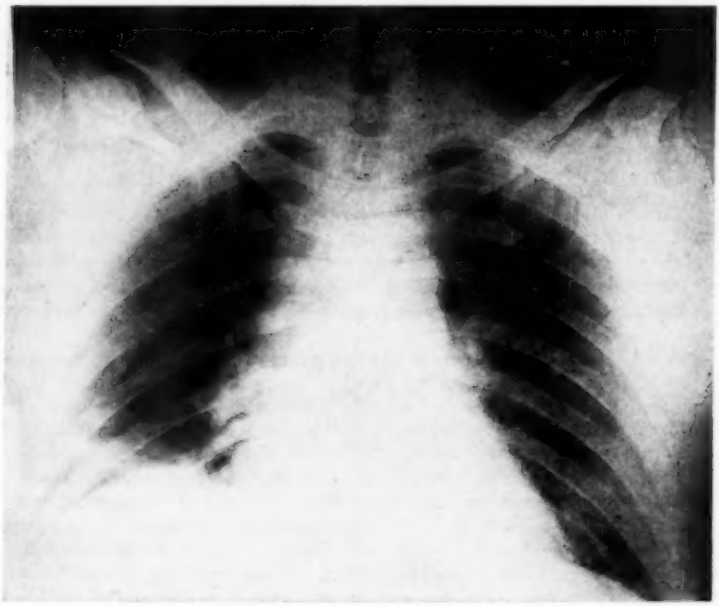

FIG. 1. Roentgenogram taken on March 3, 1947, showing an unexplained area of infiltration in the base of the right lung and an elevation of the right side of the diaphragm. Patient was asymptomatic at the time of this examination.

medical management after three months' trial, so a subtotal gastrectomy was performed. The microscopic examination of the ulcer showed no evidence of malignancy. In 1944 a hemorrhoidectomy was done because of rectal bleeding.

The patient complained of epigastric pain again in 1947, but two upper gastrointestinal series revealed no abnormality. Roentgen examination of the chest on March 3, 1947, revealed an area of stringy infiltration in the base of the right lung, accompanied by a slight elevation of the right hemidiaphragm. This was thought to be an area of atelectasis. No clinical symptoms or physical findings referable to the chest were present at that time. Because of poor health he retired from farm work in 1947 but continued to live on the farm.

On July 10, 1948, at Garfield Memorial Hospital in Washington, D. C., a routine roentgen-ray examination of the chest revealed areas of homogeneous infiltration in the periphery of the right upper lobe base and in the base of the left lung.

In October, 1948, he developed an acute illness characterized by chills, fever and cough. He was told by his family doctor that he had "virus pneumonia." Treatment with penicillin and sulfadiazine was followed by prompt subsidence of the chills and fever, but he continued to cough up small amounts of thin white sputum.

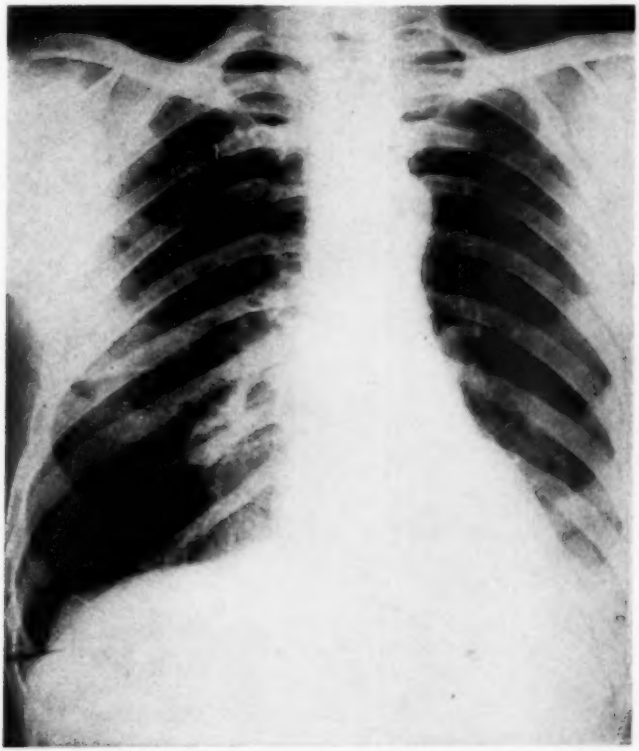

FIG. 2. Routine roentgenogram taken on July 10, 1948, showing an area of homogeneous infiltration in the base of the right upper lobe and in the base of the left lung.

The cough persisted and gradually increased in severity. There was a gradual increase in the amount of sputum, with no change in its character. He developed vague substernal pain with radiation to the right and left anterior chest. His weight fell from 150 pounds to 120 pounds during this illness and he was markedly weak, though able to be up.

In January, 1949, he experienced intense epigastric pain and was admitted to a hospital near his home for nausea and vomiting. He was transferred to Garfield

Memorial Hospital in Washington, D. C., and thence to the University Hospital.

Physical Findings: Physical examination showed an emaciated white male in marked respiratory distress. The respirations were loud and gurgling. He coughed frequently, bringing up a slightly yellowish frothy sputum which was strikingly like

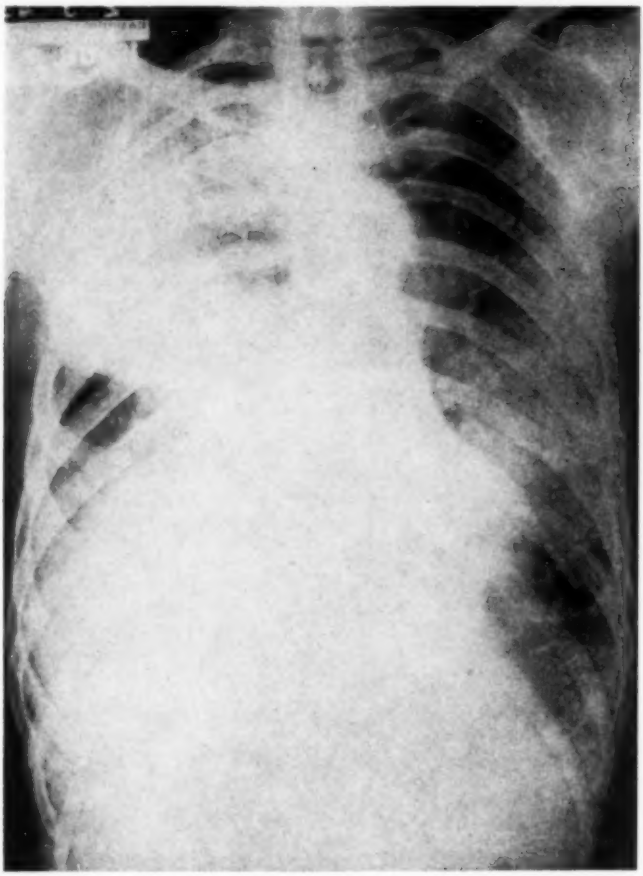

FIG. 3. Roentgenogram taken on February 3, 1950, showing a homogeneous consolidation of the right upper lobe and a partial consolidation of the right middle and lower lobes and of the left upper lobe.

soapsuds. There was no cyanosis. The finger tips were clubbed. Though markedly dyspneic, he was most comfortable flat in bed. Elevation of the head of the bed caused increase in the respiratory distress. His temperature was 98.6° F. (rectal); pulse, 85; respirations, 32, and blood pressure 102 mm. Hg systolic and 70 mm. diastolic. Other positive physical findings were limited to the lungs. There was

dullness of the percussion note at both bases and at the right apex. Rhonchi and bubbling râles obscured the breath sounds throughout both lung fields.

Laboratory Findings: Roentgen examination of the chest on February 3 and February 12, 1949 revealed a homogeneous consolidation of the entire right upper lobe and partial consolidation of the right middle and lower lobes and of the left upper lobe.

Admission laboratory studies on February 12 showed a normal urinalysis. Examination of the blood revealed a hemoglobin content of 13.6 gm. with 5,200,000 red blood cells per cu. mm. The white blood cells numbered 13,100 per cu. mm., with a differential count of 84 per cent neutrophils, 11 per cent lymphocytes, 3 per cent monocytes and 2 per cent eosinophils.

Blood chemical studies revealed a blood urea nitrogen of 25 mg. per cent and a total protein of 6.31 gm. per cent. Serum agglutinations for typhoid, paratyphoid and brucella showed no significant titer levels. The serologic test for syphilis was

FIG. 4. Gross specimens of the lungs showing the dense nodular and confluent areas of adenomatosis in the right lung and the upper lobe of the left lung. The lower lobe of the left lung is atelectatic. The right lung weighs 1,600 gm. and the left one 700 gm.

negative. The sputum showed a few gram-positive cocci and an occasional pus cell. Cultures of the sputum showed a light growth of gamma streptococci. Smears, cultures and guinea pig inoculations of the sputum were negative for tubercle bacilli.

Course in Hospital: The patient was in marked respiratory distress throughout his hospitalization, despite continuous administration of oxygen by tent. He was afebrile until the fourth hospital day, when he had a temperature elevation to 101.4° F. (rectal). He became wildly delirious and fought the oxygen tent. He developed marked cyanosis and died on the fifth hospital day.

Autopsy Findings: The important autopsy findings were limited to the lungs and pancreas.

Lungs: Gross findings: The pleura over both lungs was thickened and numerous freshly organized pleural adhesions were present throughout each pleural cavity. About 50 c.c. of blood-tinged fluid were in the right pleural cavity and about 75 c.c. of flaky greenish fluid in the left.

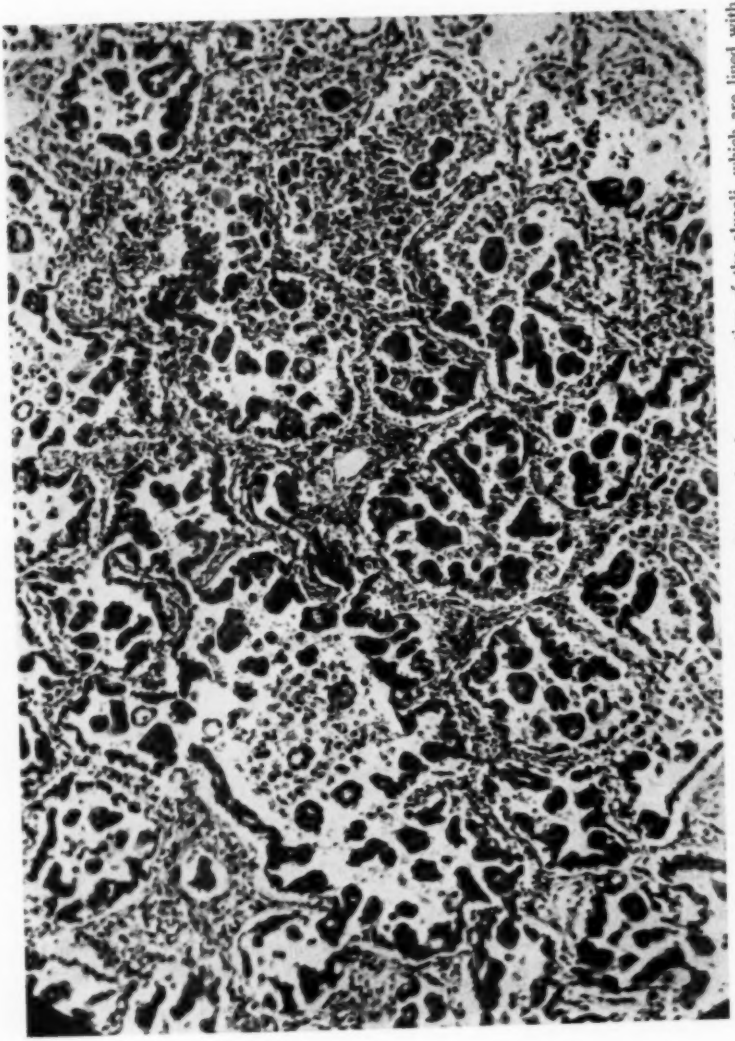

FIG. 5. Photomicrograph of a microscopic section of lung showing preservation of the alveoli, which are lined with a continuous lining of tall columnar mucus-producing cells. The cells form papillary folds into the alveoli lumen, in which there are numerous nonpigmented macrophages and isolated lining cells.

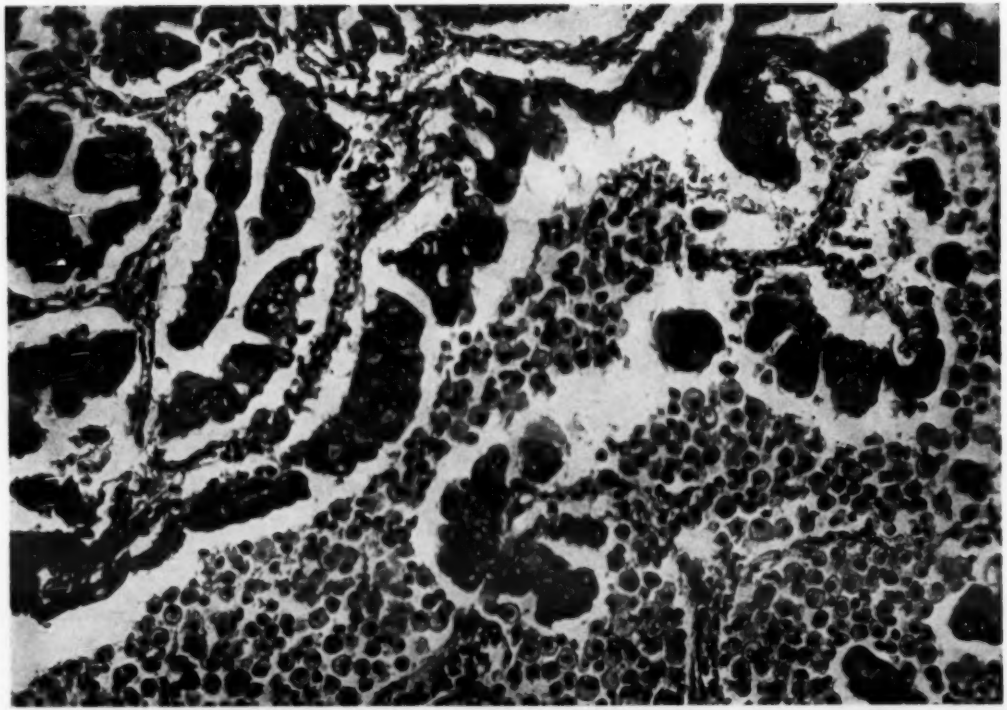

FIG. 6. Photomicrograph of a microscopic section of lung showing, at greater magnification, the continuous alveolar lining of columnar cells and the alveoli filled with macrophages and isolated lining cells.

FIG. 7. Photomicrograph of a microscopic section of lung showing the large, faintly stained degenerate bodies within the cytoplasm of the alveolar lining cells.

The right lung weighed 1,600 gm. and measured 21 by 18 by 15 cm. It was emphysematous and extended across the midline of the thorax. The entire right upper lobe was densely infiltrated by a white fleshy tumor-like mass. A smaller portion of the middle and lower lobes was also densely infiltrated by the same process. A small amount of normal appearing lung was present about the periphery of these two lobes.

The left lung weighed 700 gm. The entire left upper lobe, except for its extreme apex, was densely infiltrated by a fleshy tumor mass identical to that in the right lung. The left lower lobe was small and markedly atelectatic, with fusiform bronchiectasis of the bronchi.

Microscopic findings: The normal alveolar pattern was maintained, but the alveoli were all lined by a single layer of tall, nonciliated, mucus-producing, columnar cells. The columnar cells had an eosinophilic cytoplasm and oval basophilic nuclei, which were basally located. They were lined perpendicular to the basement membrane and did not invade the interstitial tissue, lymphatics or blood vessels. Many papillary folds of the lining cells projected into the alveolar lumen. Large degenerate bodies were present in the cytoplasm of some of these cells. In some areas the alveoli contained large numbers of nonpigmented macrophages and isolated lining columnar cells, and many others were filled with an acute inflammatory exudate. The alveolar septae were slightly thickened and infiltrated with lymphocytes. The bronchi were normal, except in the left lower lobe, where they were dilated and lined by a slightly hyperplastic pseudostratified epithelium. A marked interstitial fibrosis surrounding the bronchi obliterated the regional alveoli and contained focal collections of lymphocytes.

Pancreas: Gross findings: The pancreas weighed 125 gm. and had normal glandular architecture. There was no evidence of induration, neoplasia, hemorrhage or necrosis.

Microscopic findings: The normal lobular architecture was preserved. There was hyperplasia of the islet cells, in which there was a tendency towards acinar formation. The acini and pancreatic ducts were normal.

Review of Literature

Etiology: The etiology of pulmonary adenomatosis is unknown. Many theories have been advanced. The question of whether the disease is an inflammatory or neoplastic one arises. Until the present, the most commonly accepted theory was that the disease was inflammatory due to a specific virus or a nonspecific pulmonary irritant. However, no specific virus has been cultured from any of the reported cases, but hyperplasia of the alveolar lining does occur in response to a wide assortment of chronic pulmonary irritants.

The neoplastic theory of origin is now more widely accepted. Certain pathologic findings, such as the presence of metastases and the local occurrence of carcinomatous changes and their resemblance to reported cases of alveolar cell carcinoma, indicate a true neoplastic process.

Pathology: Pathologic changes in pulmonary adenomatosis are confined almost entirely to the lungs. The lungs are large and voluminous and do not collapse. The surface is smooth or nodular. They are quite firm and heavy, and a single lung may weigh as much as 1,700 or 1,800 gm. On cut section, the adenomatous areas are white or pinkish and extremely fleshy in appearance. Between the nodular or confluent areas of adenomatosis, areas of edema and congestion are found. In some cases the portions of the lobes not involved by the alveolar cell

hyperplasia are often practically airless, with fusiform dilatation of the bronchi. Fresh fibrinous adhesions and small granular fibrin deposits are usually found on the pleural surfaces. The pleural cavities often contain a small amount of serosanguineous fluid.

Microscopically, the normal alveolar pattern of the lungs is maintained. However, the alveoli are lined by a single layer of tall, mucus-producing, columnar epithelial cells which in most cases form papillary folds into the alveolar lumen. In a case reported by Swan [14] and another by Paul and Ritchie,[11] there were areas in which the alveoli were lined by cuboidal as well as columnar cells. In Paul and Ritchie's [11] case the columnar cells were ciliated. The alveolar lining cells are usually uniform in appearance, with only infrequent evidence of mitosis. In a few cases the cells lose all attributes of differentiation and become invasive and anaplastic.

The interalveolar connective tissue is usually slightly thickened, with an infiltration of neutrophils, lymphocytes and macrophages. The alveoli contain large numbers of phagocytes and epithelial cells. In many cases an acute inflammatory exudate is present.

In reviewing the literature Swan [14] found 27 cases reported since 1941 which fulfilled his criteria for adenomatosis. Of these 27 cases, 15 showed definite evidence of metastasis. He reported nine new cases, three of which showed metastasis. In most of the cases the metastatic adenomatous cells were found in the perivascular lymphatic channels and regional lymph nodes. However, metastases were found in bone, brain, liver and pleura.

Symptomatology and Clinical Findings: The onset is usually insidious and marked by symptoms of an acute respiratory infection. Dyspnea and cough are the most prominent symptoms, and they were present in all of the reported cases. In 50 per cent of the cases, dyspnea was the most distressing symptom. The dyspnea is due to an interference of gaseous exchange through the hyperplastic alveolar lining cells and the accumulation of a thick tenacious sputum in the bronchi. The dyspnea is often out of proportion to the roentgen changes. The cough is often of two to three years' duration and, though frequently dry at first, later becomes productive of a copious amount of watery mucoid or soapsuds-like sputum. This sputum is a very characteristic finding. The sputum is negative for acid-fast bacilli and other constant invaders. Hemoptysis is occasionally a late finding. Repeated attacks of acute pneumonia are common, and this is an important diagnostic finding. Other frequent symptoms, which have no specific diagnostic importance, are a loss of weight, anorexia and cold sweats. The most consistently found physical findings are a clubbing of the fingers and toes and cyanosis of the nails and mucous membranes. The chest is usually asymmetrical, with a limited expansion and an inspiratory retraction of the ribs. There are often increased resonance, tactile fremitus and signs of pleural effusion. The white blood count is usually increased.

The disease may occur at any age but is most common in the carcinoma age period. Cases are reported in patients between the ages of 21 and 79 years, with an average age of 47 years. The sexes are about equally represented. The disease is usually of about nine months' duration. One patient had persistent symptoms two and one-half years before death.

Roentgen Changes: Roentgen changes in pulmonary adenomatosis are not characteristic. However, according to Paul and Ritchie,[11] the pulmonary lesions fall roughly into two groups or more, commonly a combination of the two: (1) A large area or areas of soft, rather homogeneous infiltration, resembling that of an inflammatory consolidation. The area or areas are not usually lobar in distribution but are often extensive and bilateral, and involve most of the lung fields. Atelectasis is not a prominent feature and is important in ruling out bronchogenic carcinoma when the disease is limited to one lung. Terminally, clinical signs of infection are encountered and the diagnosis of pneumonia is most often made. (2) Small, soft, patchy, nodular, widely disseminated areas of infiltration. These patchy areas are usually ill-defined and often confluent. They are scattered throughout both lungs. This type of lesion may simulate metastatic carcinoma, tuberculosis, bronchopneumonia, sarcoidosis, silicosis, coccidioidomycosis and Hodgkin's disease. (3) A combination of these two types of pulmonary lesions.

Therapy: Therapy for pulmonary adenomatosis has been entirely symptomatic. Wood and Pierson[16] did a lobectomy on a case with only radiographic involvement of the right lower lobe. However, the patient died five months later with generalized pulmonary involvement, which included mediastinal nodes, and widespread metastatic lesion from carcinoma of the cervix. Swan[14] reports a case, treated by pneumonectomy, who died six months later with a massive pleural effusion. No autopsy was performed on this case, but there was no clinical evidence of recurrence. In another case reported by Swan,[14] the patient was treated by lobectomy and was still surviving two years later, with no clinical evidence of further involvement.

No evidence of the use of roentgen therapy was found. However, since the cells are so well differentiated, it is unlikely that irradiation will be of much benefit except in those cases in which anaplasia and other evidences of malignancy have developed.

Discussion

The clinical, pathologic and roentgen findings in this case of pulmonary adenomatosis are similar to those of other reported cases. However, there are three unusual findings in our case: (1) unexplained roentgen changes in the lungs two years prior to death; (2) the presence of large, faintly stained homogeneous bodies in the cytoplasm of many of the alveolar lining cells, and (3) the hypertrophy of the islet cells of the pancreas, with a tendency toward acinar formation. In none of the cases reviewed were there demonstrable roentgen changes in the lungs two years prior to death. The latter two findings have each been previously reported in single cases. Norris[9] found large homogeneous bodies in the cytoplasm of the alveolar lining cells in a case of adenomatosis occurring in a guinea pig, and Alexander and Foo Chu[1] found an adenoma of the islet cells of the pancreas in their case.

A clinical diagnosis of pulmonary adenomatosis should be suspected in cases with: (1) a chronic pulmonary disease in which there are repeated attacks of acute pneumonia; (2) a nonspecific patchy or homogeneous infiltration on the roentgenogram, and (3) the production of a large amount of thin, watery, mucoid, "soapsuds-like" sputum.

Summary

A case of pulmonary adenomatosis and a brief review of the literature on this disease are presented.

Addendum

Since the acceptance of this article for publication, C. A. Good et al. have reported upon 12 cases of alveolar cell tumors of the lung seen at the Mayo Clinic. In this article the authors stressed the cytologic examination of the sputum and bronchial secretions as a valuable aid in the detection and diagnosis of alveolar cell tumors. Cytologic examination of the sputum and bronchial secretions was performed in six of their 12 cases. Positive results were reported in four of the six cases examined and in retrospect one of the cases reported as negative would at the present time be reported positive. In two of the four cases that were reported as showing the presence of neoplastic cells it was suggested that these cells were of the alveolar cell type.

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CORONARY EMBOLISM (INTRA VITAM DIAGNOSIS) AND NECROTIZING RENAL PAPILLITIS: CASE REPORT *

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MASSIVE coronary embolism is an uncommon occurrence which usually produces sudden death. When death is delayed, coronary embolism is seldom suspected; and, if the patient survives, the diagnosis cannot be proved. In few reported cases have electrocardiograms following coronary embolism been made, and in only one of these was the correct diagnosis made during life.[1]

In the case presented, the appearance of electrocardiographic signs of myocardial infarction and complete auriculoventricular block during the course of septicemia, in a diabetic aged 24 years, permitted the diagnosis of coronary embolism, which was confirmed at necropsy. Unexpected findings at autopsy were necrotizing renal papillitis, which is rare at this age, and intercapillary glomerulosclerosis, which is uncommon in young persons with diabetes of short duration.

CASE REPORT

A 21 year old white male was inducted into the Army in January, 1946. One month later he was hospitalized for a minor ailment and was found to have diabetes mellitus. He was subsequently admitted to Aspinwall Veterans Hospital in May, 1946, for control of diabetes, and in October, 1947, and September, 1948, for ulcer of a toe. During these admissions the patient disregarded dietary restrictions and control of the diabetes proved difficult; an average of 50 units of an insulin mixture was required daily. The heart was normal on physical and roentgenographic examination. Blood pressure was 105/75, 130/90 and 118/98 mm. Hg on the first, second and third admissions, respectively. In October, 1947, bilateral diabetic cataract was found. The urine persistently showed albumin (averaging a "trace" during the first admission, 1 plus during the second, and 2 plus during the third), and occasional pus cells and erythrocytes. Plasma proteins, blood non-protein nitrogen and urinary concentrating power were normal. When not in the hospital, the patient took insulin but did not adhere to the diet prescribed.

The final admission, at the age of 24, began on March 8, 1949. Five weeks previously, the patient had developed shaking chills, which recurred every second day; severe headache, which recurred daily, and persistent vomiting. He continued to take insulin. A few days before entry, pain in the hips and knees appeared. There had been no preceding ulcerations or sore throat.

On admission, the patient was acutely ill. The temperature was 99.6° F., rising a few hours later to 103.6° F. A soft apical systolic murmur was noted. Blood pressure was 130/90 mm. Hg. During hospitalization fever persisted, the heart became larger, the apical systolic murmur louder, and a systolic blowing murmur became audible at the aortic area; petechiae appeared, and blood cultures yielded numerous colonies of *Staphylococcus aureus hemolyticus*. A diagnosis of acute bac-

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terial endocarditis was made. An electrocardiogram on March 10 showed sinus tachycardia. On the night of March 13 the temperature was 106.0° F.; the cardiac rhythm was irregular, with ventricular rate of 118 per minute and a pulse deficit. An examiner, believing auricular fibrillation to be present, administered 1.2 mg. digitoxin intravenously. An electrocardiogram the following morning showed sinus tachycardia at a rate of 143 per minute, complete auriculoventricular block, idioventricular rhythm from a nodal pacemaker at a rate of 93 per minute, and evidence of recent posterior myocardial infarction. A diagnosis of coronary embolism was made. The patient received no more digitalis. Electrocardiograms on March 15 and 16 showed complete auriculoventricular block; on March 18, coronary sinus rhythm with PR interval of 0.08 second; and on March 19, 21 and 24, normal sinus rhythm with PR intervals of 0.33, 0.28 and 0.28 second, respectively. Representative tracings are

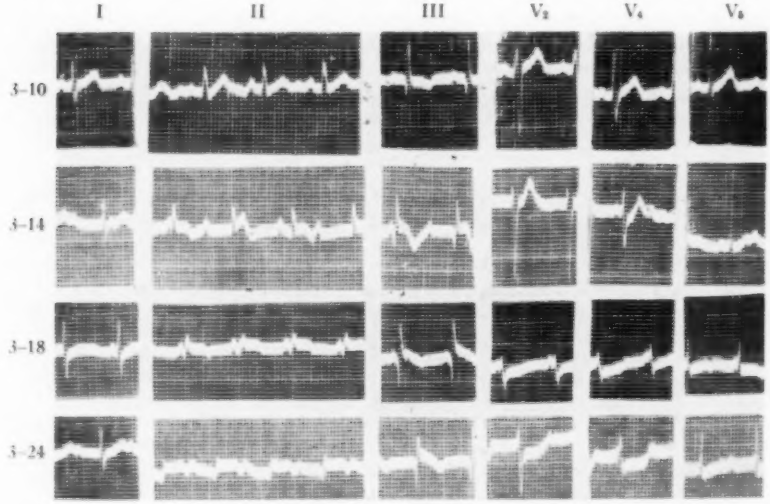

FIG. 1. Electrocardiogram on March 10 shows sinus tachycardia. Subsequent electrocardiograms reveal evidence of posterior myocardial infarction. On March 14 there is complete auriculoventricular block with ventricular rate of 93 per minute; on March 18, coronary sinus rhythm, and on March 24, partial auriculoventricular block.

shown in figure 1. Unipolar extremity leads (not reproduced) confirmed the diagnosis of posterior myocardial infarction. ST segment deviations became more pronounced. Blood pressure ranged from 120/75 to 130/80 mm. Hg. The patient at no time complained of chest pain.

The urine showed glucose, albumin in small amounts, small to moderate numbers of erythrocytes and pus cells, and occasional casts. Blood non-protein nitrogen on admission was 42 mg. per 100 c.c., but rose terminally to 134 mg. per 100 c.c. Serum albumin measured 2.9 gm. and globulin 3.5 gm. per 100 c.c. on the day before death.

Treatment included penicillin, caronamide, sulfadiazine, streptomycin, aureomycin and parenteral fluids. The diabetes was controlled with insulin. Blood cultures became sterile and the temperature remained normal after March 23, but the patient vomited repeatedly, became very edematous and failed steadily. He died on March 26, the nineteenth hospital day.

Autopsy (pertinent findings): The heart weighed 400 gm. On the aortic valve cusp overlying the right coronary orifice was a large, fungating vegetation. The right coronary artery was occluded, 6 mm. from its origin, by an elongated red embolus with pus at its distal end. The other coronary arteries contained patchy atheromata which did not compromise the lumina. Fully half of the posterior portion of the interventricular septum was comprised of patchy, yellow-white areas, some with dark red borders, all fairly firm (figure 2). The left ventricular wall measured 15 to 18 mm. in thickness. Blood taken from the heart was sterile on culture.

FIG. 2. Heart showing lesion of aortic valve and septic myocardial infarction.

The kidneys (figure 3) were swollen, the left weighing 200 gm., the right 250 gm. Their surfaces were a mottled yellow-red. The pelves and calyces contained pus. The tips of the pyramids were black and necrotic. An area of hemorrhage was seen in the upper calyx of the left kidney, and small abscesses were found on the outer surface of the lower pole of the right kidney. The ureters were normal.

The lungs were edematous and showed patchy areas of bronchopneumonia. The spleen, which weighed 225 gm., was soft and contained two abscesses. The legs were edematous. Each pleural cavity contained approximately 500 c.c. and the abdominal cavity approximately 3,000 c.c. of clear yellow fluid. The other organs were not remarkable.

On microscopic examination, the heart showed multiple small abscesses in which

bacteria were seen; there was marked fragmentation of the surrounding myocardial fibers. A section through the right coronary artery showed the lumen to be filled by a recent embolus. The aortic valve cusp showed a relatively avascular fibrinous vegetation, with occasional clumps of polymorphonuclear leukocytes and some bacteria.

A section through the tip of a renal papilla (figure 4) showed a sharply demarcated zone of necrosis with degeneration of tubules, interstitial edema and comparative lack of cellular exudate. There were a few capillaries with hyalinized thrombi. Some of the tubules in the papilla were filled with degenerating leukocytes. Throughout the cortex, there were uniformly severe hyaline thickening and degeneration of the arterioles, with severe endothelial swelling frequently all but occluding the lumina. Some glomeruli were hyalinized and surrounded by areas of fibrosis and

FIG. 3. Kidney showing necrotizing papillitis and inflammatory reaction of pelvis.

atrophic tubules; others showed thickening of the basement membrane of the capillaries and capsule, sometimes with simplification of the tufts, and were bloodless; some glomeruli were intact and congested; some showed an excess of polymorphonuclear leukocytes. A few glomeruli showed nodular hyalinization of the peripheral tufts such as is seen in intercapillary glomerulosclerosis (figure 5). One section showed a large cortical abscess; the interlobular artery at the apex of the abscess showed severe panarteritis and marked intimal fibrosis, and one branch was completely occluded by an organized thrombus. The proximal convoluted tubules uniformly showed severe vacuolar degeneration and swelling. The interlobular and arcuate arteries, except for the one instance, showed little or no thickening.

FIG. 4. Photomicrograph showing necrotizing renal papillitis.

The pancreas showed very few islets. Many acini were dilated, contained inspissated secretion and showed flattening of the epithelium.

DISCUSSION

The scant number of reported cases of gross coronary embolism hardly reflects the true incidence of this occurrence.[2] A review of approximately 60 proved (and hence fatal) reported cases gives a probably distorted view of the course following gross coronary embolism, but it is significant that, although most of the patients died suddenly and often instantaneousiy, some lived for several days after the onset of chest pain, and in six previous cases, as well as our own, there was no chest pain, although death occurred gradually. How often recovery occurs following coronary embolism is not known, but probable instances have been reported;[2, 3] and now that bacterial endocarditis, the condition most commonly giving rise to coronary embolism, is no longer invariably fatal, such recoveries may be more common. Since gross embolism may be symptomless,[4] it

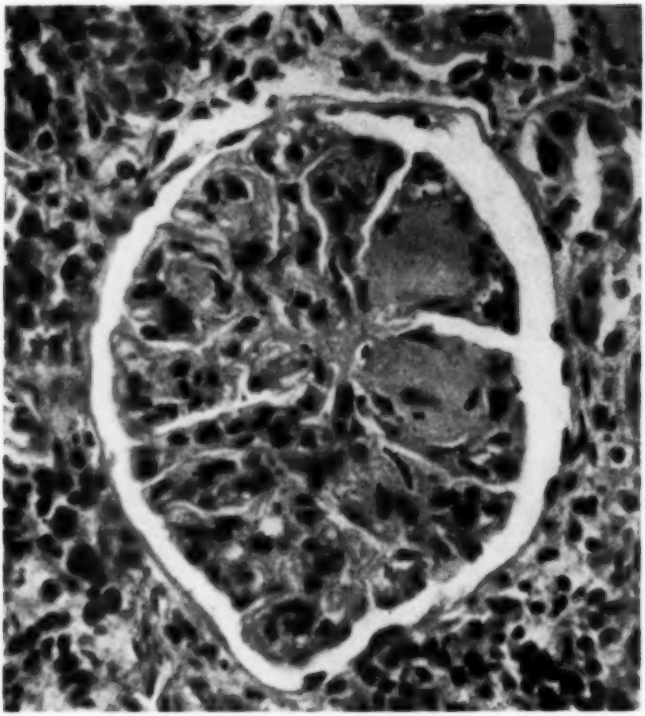

FIG. 5. Photomicrograph showing intercapillary glomerulosclerosis.

follows that patients with bacterial endocarditis should have electrocardiograms taken frequently and, if coronary embolism is suspected, massive doses of antibiotics should be given to try to prevent the development of myocardial abscesses and mycotic aneurysm.

In the case presented there was no chest pain at any time, but the electrocardiographic signs of myocardial infarction in a young person with bacterial endocarditis suggested the diagnosis of coronary embolism. Complete auriculoventricular block due to coronary embolism has not heretofore been reported. It seems unlikely that the block was due to digitoxin. The rapid ventricular rate in the presence of complete heart block was probably due to the high fever. The presence of pus at the distal end of the occluding lesion confirmed its embolic character. The survival for 12 days after signs of myocardial infarction appeared is noteworthy.

Recent studies[5, 6, 7] have established that necrotizing renal papillitis is an extremely serious and not uncommon complication in diabetics, but it is said to

be "exceedingly rare" in patients under 40 years of age.[6] Ischemia of the pyramids is believed by some [5, 6] to be an important factor in the development of the lesion, and in our patient the severity of renal vascular disease was striking. Intercapillary glomerulosclerosis might also tend to decrease pyramidal blood flow. Localization of necrosis to the tips of the papillae, as was found in this case, is uncommon, and especially so among diabetic patients;[6] perhaps antibiotics may have hindered the development of more widespread lesions.

Intercapillary glomerulosclerosis is likewise an unusual pathologic finding in individuals under 30 years of age,[8] and is more apt to occur in persons with diabetes of long duration.[9, 10] It is still not known how long a time is required for the development of this lesion, but its presence in a young person with diabetes of presumably two years' duration is evidence that intercapillary glomerulosclerosis may develop rapidly.[11]

SUMMARY

A patient aged 24 years, with diabetes mellitus of two years' duration, developed acute bacterial endocarditis. A diagnosis of coronary embolism was made when electrocardiographic signs of myocardial infarction and complete heart block developed, although the patient had no chest pain. Autopsy revealed septic myocardial infarction due to coronary embolism and, in addition, necrotizing renal papillitis and mild intercapillary glomerulosclerosis. The significance of these findings is discussed briefly.

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KALA-AZAR (VISCERAL LEISHMANIASIS): REPORT OF A CASE WITH 34 MONTH INCUBATION PERIOD AND POSITIVE DOAN-WRIGHT TEST *

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SINCE World War II there have been numerous reports of the occurrence of kala-azar in service men returning from endemic areas in the Mediterranean coastal countries,[1, 2, 3, 4, 5, 6, 7] India and North China.[13, 14] To our knowledge, there has been no report of a case contracted within the United States.

The minimal incubation period in 22 cases reviewed by the authors varied between one [11] and 23 [7] months. Ecker and Lubitz [11] state that it may vary from two weeks to more than a year, with an average of from two to four months. However, the length of the incubation period is often only presumptive, because of the difficulty in determining the exact time of inoculation and the frequently insidious onset of the illness.

Significant diagnostic features of the disease include fever and chills of obscure origin,[1, 3, 4, 5, 6, 7, 8, 9, 14] occasional double or triple daily rise of temperature,[1, 3, 6, 11] tendency to remarkably little prostration until late in the course of the disease,[3, 6, 9, 11] increased serum globulin and a decreased serum albumin,[1, 3, 11, 16, 18] enlarged liver [1, 3, 6, 7] and/or spleen [1, 2, 3, 6, 7, 9, 10, 11, 12, 18] with evidence of hypersplenism, including mild to moderate anemia,[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18] leukopenia [2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 15, 17] and thrombocytopenia. Hemorrhagic phenomena may occur as a result of the latter.[4, 7]

The following case is presented because of its unusually long incubation period, the positive Doan-Wright test,[19, 20] indicating hypersplenism, the modified culture medium employed in isolating the organism, and the differential diagnostic problem involved.

CASE REPORT

A 25 year old veteran was admitted to the Veterans Administration Hospital, Oklahoma City, Oklahoma, March 23, 1949, for treatment of chills and fever. Except for postocular headaches, which had occurred in the afternoon for approximately one year, he had been apparently well until October, 1948, five months before his admission. At that time he first noticed mild epigastric distress in the midmorning and midafternoon described as a "rumbling and feeling of hunger." This discomfort was relieved by eating. Two or three weeks later he began noticing weakness in the afternoons. He thought he had a fever but did not take his temperature. On two occasions the weakness was so pronounced that he stopped work and went to bed. A few days later a severe chill occurred. His afternoon weakness and fever con-

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tinued. Three weeks after the first chill a second chill occurred. A third such attack appeared one week after that. He entered a local hospital and a clinical diagnosis of malaria was made. He was given oral quinine, atabrine and, later, intramuscular quinine, without noticeable effect. He left the hospital and consulted another physician, who began a series of four arsenical injections on the basis of a clinical diagnosis of malaria. The injections were not completed, it was said, because of technical difficulties. The patient consulted a third physician, who examined a peripheral blood smear and diagnosed malaria. He started treatment with quinine and atabrine. Slight temporary improvement in subjective symptoms occurred, but the patient continued to have chills almost daily.

Epistaxis occurred on three occasions at night. Night sweats were prominent from the onset. On March 23, 1949, bright red blood was seen in the stool. He then recalled having seen occasional dark, tarry spots in the feces two weeks previously. He lost 15 pounds of weight during the first month of his illness.

His record shows that he had served two years in the Mediterranean theater from February 1, 1944, to January 12, 1946. While in Italy he spent two months in Bari, two months in Caserta, three months in Foggia, and six months in a camp outside of Naples. He was apparently well at the time of discharge from service on January 30, 1946.

Physical Examination: Examination revealed a pale, poorly nourished, chronically ill white male, appearing his stated age of 25. The eye, ear, nose and throat examination, including funduscopic, was normal. The teeth were poorly kept, but there was no evidence of gum infection or bleeding. The chest was well developed

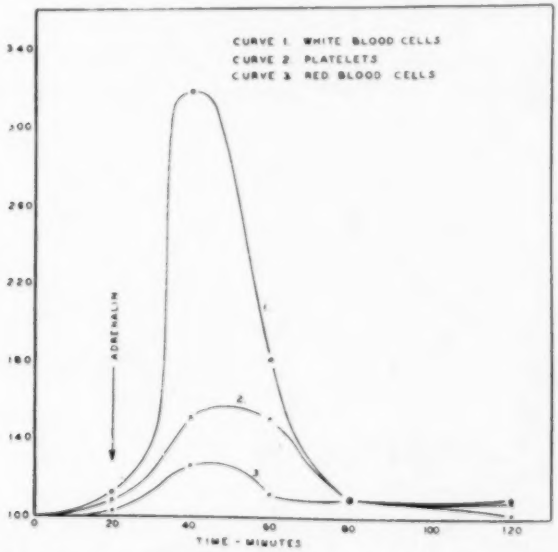


FIG. 1. Positive Doan-Wright test for hypersplenism, illustrating temporary increase in blood elements following adrenalin injection. Graphed in percentage of initial counts (red cells, 3,500,000; white cells, 1,450; platelets, 60,000).

and symmetrical. Expansion was equal bilaterally. Percussion and auscultation were normal. The cardiac apex impulse was felt 2 cm. to the left of the midclavicular line in the fifth interspace. Heart sounds were normal. The blood pressure was 120 mm. Hg systolic and 85 mm. diastolic. There was a visible fullness in the left upper quadrant of the abdomen. The spleen was palpable and firm and extended to the level of the umbilicus. The liver was palpated two fingerbreadths below the costal margin in the right midclavicular line. The external genitalia, rectum and

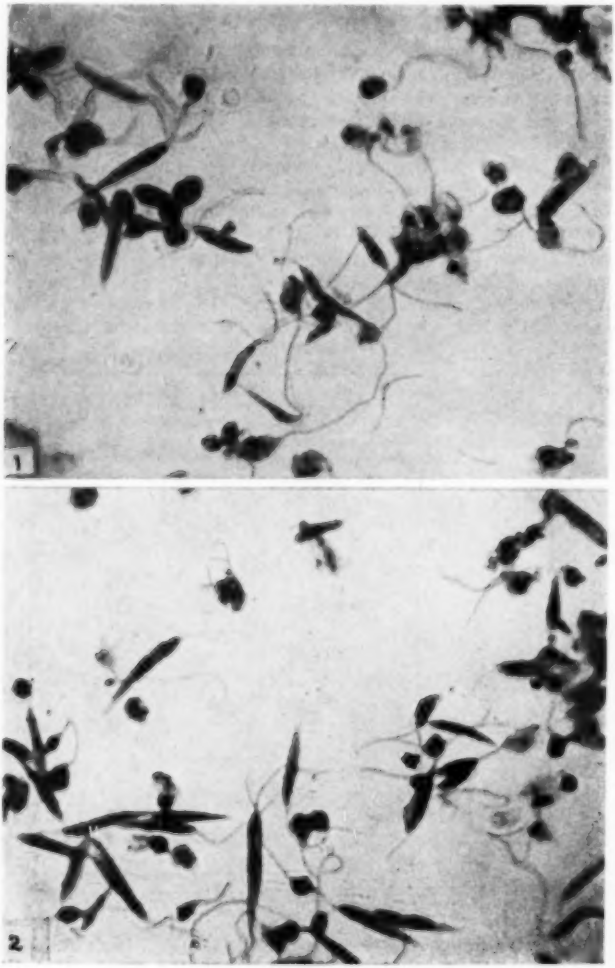
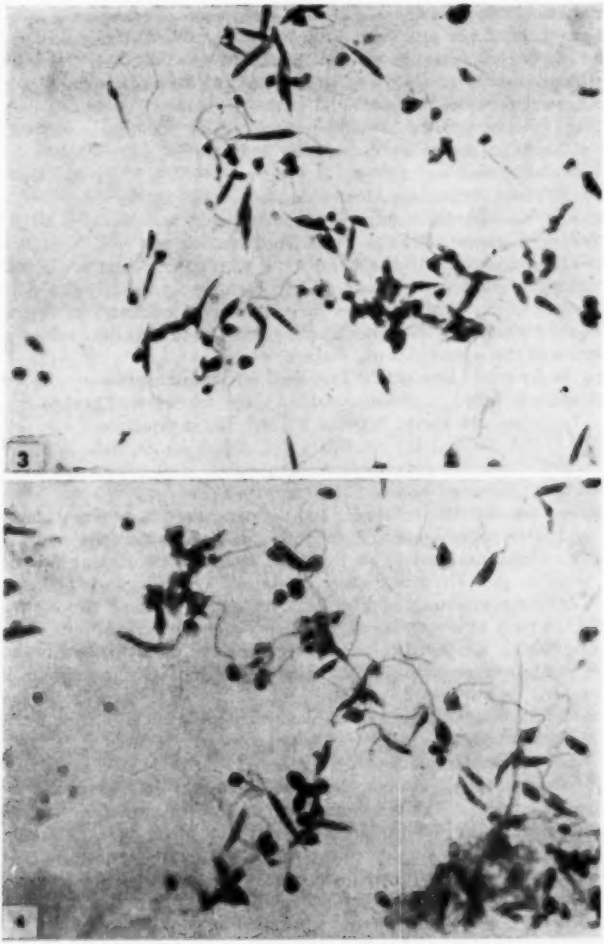


FIG. 2A



B

FIG. 2, A and B. *Leishmania donovani* in culture. Note variations in size and shape, with transitions from the Leptomonas form to others more resembling the Leishman-Donovan bodies often seen in spleen and marrow cells. The kinetoplast at the blunt anterior end, with its flagellum, is evident. Tendency to formation of agglutination rosettes may also be observed. 1 and 2, 1,400 ×; 3 and 4, 900 ×, oil.)

prostate were normal. The lymph nodes were not noticeably enlarged. The musculoskeletal system was grossly normal. Neurologic examination was negative.

Laboratory: On admission his red blood count was 3,000,000, his white count, 1,700 (a letter from his doctor reported a white blood count of 8,000 on March 21,

1949); the hemoglobin was 9.5 gm.; a differential count was reported as 3 per cent juvenile neutrophils, 2 per cent stabs, 30 per cent segmented forms, 57 per cent lymphocytes and 8 per cent monocytes; the platelet count was 148,000. The sedimentation rate was 116 mm. per hour (Westergren method). No malarial parasites were seen on repeated examination of the blood and sternal marrow. The icterus index was 6. Red cell fragility was reported as within normal limits. The mean corpuscular volume was 103 cu. μ; the mean corpuscular hemoglobin, 32 micromicrograms. A cephalin flocculation test was reported 4 plus in 48 hours. Agglutination tests for typhoid, paratyphoid, brucellosis, tularemia, heterophil antibodies, *Proteus* OX-19, and *Proteus* OX-2 were all negative. Serum albumin was reported as 3 gm., and serum globulin, 5.7 gm. per 100 c.c. A serum diagnostic test with Neostibosan * was strongly positive. No antimalarial therapy had been given recently. Urinalysis was negative, except for a trace of albumin. Chest roentgenogram showed a normal heart and lungs, except for a slight increase in peribronchial markings in the right base. Flat film of the abdomen showed splenic enlargement, with indistinct left psoas margin and depression of the splenic flexure of the colon.

Course in Hospital: During the first week of hospitalization a daily double rise of temperature was noted on three occasions. The temperature ranged from 97° to 105° F. The pulse rate varied between 80 and 100 per minute. The white blood count on the fourth hospital day reached a low of 700 per cu. mm., with 50 per cent neutrophils and 30 per cent lymphocytes. Thereafter, until treatment was begun, the white blood count remained between 1,200 and 2,400.

Because of the extreme leukopenia and the patient's serious illness, he was given penicillin and later sulfadiazine and sulfamerazine prophylactically and empirically. A consultant ordered aureomycin on the same basis, but the patient did not respond to any of these drugs. His temperature continued. The diagnosis of kala-azar was considered, but no organisms could be found in studies of the bone marrow smears. On April 4, 15 days after admission, the serum albumin was 3.2 gm. and globulin, 7.5 gm. per 100 c.c. On April 6, small petechiae were noted in the conjunctiva and on the soft palate. Examination at that time revealed a systolic murmur at the left third interspace.

Because of the splenomegaly and the panhematopenia, an adrenalin test for hypersplenism, using a modified Doan and Wright procedure,[19, 20] was performed on April 8. After baseline counts had been determined, 1 c.c. of 1:1,000 adrenalin was administered subcutaneously. A complete blood count was done every 20 minutes for one and one-half hours. The red count rose to 125 per cent, the platelet count to 150 per cent and the neutrophil count to 318 per cent of the baseline pre-test counts. (See figure 1.) This was considered a positive test for hypersplenism.

On the day of the adrenalin test, and for a week thereafter, the temperature rose again and reached daily peaks of from 103° to 104.6° F.

On April 19, 1949, another sternal puncture was done and a culture of the marrow was made, using a special modification of NNN medium. On April 28, thirty days after admission, the culture was reported as positive for *Leishmania donovani* (figure 2). Subsequent search of the bone marrow smears revealed Leishman-Donovan bodies there.

The patient was treated with Neostibosan, beginning with 0.1 gm. the first day, 0.2 gm. the second day, and 0.3 gm. daily thereafter until a total of 3 gm. was given. The medication was started intramuscularly but, because of local discomfort, was continued by the intravenous route. Six days after the treatment was started the

* Neostibosan—brand of ethylstibamine (organic pentavalent antimony complex), Winthrop Chemical Company, Inc.

temperature returned to normal and remained normal throughout the remainder of his hospital stay. On May 8, ten days after treatment was started, the laboratory reported 3.2 gm. serum albumin and 5.3 gm. serum globulin per 100 c.c.

By June 1, physical examination showed marked improvement in color, strength and vigor. The spleen was palpated two fingerbreadths below the costal margin but was not tender. The red blood count was 4,370,000; white count, 6,400; hemoglobin, 12.5 gm. The platelet count at that time was 110,000, as compared to 50,000 to 60,000 at the beginning of treatment. The petechiae had disappeared.

By July 21, 1949, three months after treatment, the patient had gained 17 pounds and felt well. During the seven weeks following his discharge from the hospital his appetite had been good. There had been no complaints referable to the abdomen, and no fever. Physical examination revealed normal heart and lungs. The abdomen

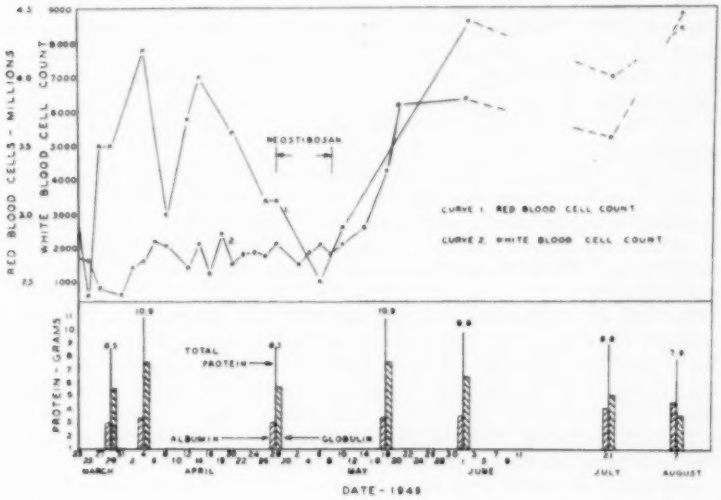


FIG. 3. Graphic presentation of red and white counts, total protein, albumin and globulin determinations before and during the period of treatment and convalescence.

was soft. There was no tenderness, and the spleen could not be felt. The red blood count at that time was 4,100,000; white count, 5,000; hemoglobin, 11.5 gm. Differential revealed 50 per cent neutrophils and 48 per cent lymphocytes. Platelet count was 110,000. Sedimentation rate (Westergren) was 63 mm. per hour. Cephalin flocculation test at that time was 4 plus in 48 hours. Icterus index was 8.

At the time of his last reëxamination on September 7, 1949, four months after completing treatment, he had maintained his weight at 150 pounds. He felt well, had a good appetite and was working every day. Physical examination was essentially negative. Red blood count was 4,400,000, with 14.5 gm. of hemoglobin. The white blood count was 8,900, with 78 per cent neutrophils and 28 per cent lymphocytes. Platelet count was 130,000, and sedimentation rate was 13 mm. per hour. Urinalysis revealed a trace of albumin but was otherwise negative. There were 4.3 gm. serum

albumin and 3.4 gm. serum globulin per 100 c.c. Cephalin flocculation test showed only a trace in 48 hours. Figure 3 summarizes the response to therapy.

Discussion

This patient was admitted to the hospital for management of chills and fever of undetermined origin. Previous diagnoses of malaria had been made, one physician reporting a positive blood smear. The patient had not responded to several courses of antimalarials. The diagnosis of malaria could not be confirmed at this hospital.

Because of the large spleen and the low white count, granulocytopenia, leukemia, Hodgkin's disease, kala-azar and primary splenic neutropenia were considered diagnostic possibilities.

The bone marrow cytology and differential count were essentially normal. No nodes were available for biopsy. The positive Doan-Wright test was considered good evidence for splenic neutropenia, although the differentiation between primary hypersplenism and secondary hypersplenism could not be proved. A serum diagnostic test for kala-azar with Neostibosan was reported positive. However, no Leishman-Donovan bodies were seen on early examinations of bone marrow smears.

The patient was presented at staff meeting and it was felt that the most probable diagnosis at that time was that of a splenic neutropenia. It was suggested that penicillin be continued prophylactically. Further blood cultures, bone marrow smears and cultures, and trial therapy of aureomycin were suggested. Sulfonamides, penicillin and aureomycin were equally unsuccessful in affecting the temperature.

On April 28, 1949, one month after admission and six months after onset of symptoms, a bone marrow culture was reported positive for *L. donovani*. Two cultures were run in parallel. One was the usual NNN medium made with defibrinated rabbit blood; the other was prepared with defibrinated blood from the patient. Positive culture was obtained only from the latter. Lloyd, Napier and Paul, quoted by Strong,[21] feel that the high globulin and low albumin of the blood serum is favorable to the growth of the organisms.

Treatment with a single course of Neostibosan (total dose, 3 gm.) was successful, and subsequent examinations to four months following treatment have shown no evidence of recurrence.

Laboratory proof of the diagnosis was of primary importance, as definitive treatment was then possible and a splenectomy was avoided. Later it proved to be of considerable economic value to the veteran in obtaining service connection in the face of the unprecedented incubation period.

Summary

1. A case of kala-azar (visceral leishmaniasis) is presented.
2. A minimal incubation period of 34 months is recorded.
3. A positive Doan-Wright test for splenic neutropenia was obtained.
4. Parallel bone marrow cultures were negative on regular NNN medium, positive on modified NNN containing defibrinated blood from the patient.
5. Successful treatment with a single course of Neostibosan (3 gm.) was indicated by a four month follow-up period.

ACKNOWLEDGMENT

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14. Scavel, F. G.: Kala azar in China—clinical observations, Ann. Int. Med. **21**: 607–627, 1944.
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17. Sen Gupta, P. C., and Chakravarty, N. K.: Agranulocytosis in kala azar, Indian M. Gaz. **82**: 11–16, 1947.
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19. Doan, C. A., and Wright, C. S.: Primary congenital and secondary acquired splenic panhematopenia, Blood **1**: 10, 1946.
20. Wintrobe, M. W.: Clinical hematology, 1946, Lea & Febiger, Philadelphia, p. 767.
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EDITORIAL

HEMOSIDEROSIS AND THE PARENTERAL ADMINISTRATION OF IRON

THE extensive deposition of hemosiderin granules in the cells of the liver and other organs is known to occur in three clinically distinct pathologic states: In idiopathic hemochromatosis, in severe malnutrition with pellagra as observed in South African negroes, and following repeated transfusions of blood. It now seems certain that this may also be brought about by the excessive or protracted parenteral administration of iron. As commercial preparations of iron are now available which can be administered intravenously in effective doses without causing immediate severe reactions, the possible harmful effect of such pigment promises to become a question of immediate practical importance.

There are sharp differences of opinion as to the direct pathogenic effects of hemosiderin, and a final answer can not yet be given. Some conclusions may be drawn, however, from a study of these pathologic states and from a consideration of what is known regarding the metabolism of iron. Recent experiments using iron labeled with radioactive isotopes have done much to clarify the latter problem and have confirmed many of the fundamental observations of Whipple and other earlier workers.

The amount of iron in the average daily diet, about 10 to 15 mg., is minute compared with the total amount in the body, about 4.5 gm., the bulk of which is in the hemoglobin of the red cells. The body has become adapted to this situation by a mechanism which tenaciously retains the iron after its absorption. There is no effective means by which an excess of iron can be excreted, and appreciable amounts are lost only as a result of hemorrhage or pregnancy. Such losses doubtless explain the rarity of hemochromatosis in women. The small amount lost in the feces (believed to be about one milligram per day) probably comes largely from desquamated epithelium and is replaced by absorption of a corresponding amount, and usually no more, from the food.

Iron is absorbed in the ferrous state, mainly in the proximal part of the duodenum. After entering the mucosal cell it is oxidized to the ferric state and combined with a specific crystallizable protein, apoferritin, to form ferritin. Iron in this form does not give the prussian blue reaction. Ferritin is also found in the cells of the liver and many other tissues and normally constitutes the bulk of the stored iron in the body.

To satisfy the needs of the tissues and replenish the stores, iron is given up by the ferritin in the mucosal cell and (supposedly in the ferrous state) passes into the blood where it combines with another specific protein, siderophilin, a β_1 globulin present in Cohn's fraction IV–7. This is the only known vehicle for the transport of iron, and it also carries the traces

of copper present in the blood. Normally the amount of iron in the plasma is about 100 γ per cent. The siderophilin is capable of carrying 300 γ per cent and is only a third saturated. In the tissues iron is taken up by the cells where it may be immediately utilized or stored as ferritin.

The body is normally protected from an excess of iron by limitation of its absorption. It would be tempting to assume that the concentration of iron in the plasma was the factor controlling absorption, but this has proved not to be the case. Thus Dubach et al.[1] have shown that neither increasing the amount of siderophilin by preliminary injections nor saturating the siderophilin by intravenous injection of iron alters the rate of absorption of radioiron subsequently administered orally. The rate of absorption varies with the amount of iron stored in the tissues, not with the concentration in the plasma or the degree of anemia, if any. The control is exercised in the intestinal mucosal cells, the "mucosal block." Here precise information ends, but one may speculate (Granick[2]) that the amount absorbed varies with the degree of saturation of the cell with ferritin and with the rate of discharge into the blood. The latter may be stimulated by anoxia resulting from anemia, but the correlation with the degree of anemia is not close. Anemia caused by acute hemorrhage in a normal animal does not increase the rate of absorption until sufficient time has elapsed to permit depletion of the body stores.

Although the control so exercised is relatively effective, it appears not to be so nearly perfect as has often been assumed. Dubach et al.[1] administered radioiron orally in a dose of 1 mg. per Kg. and measured the amount unabsorbed in the feces as well as that appearing in the red blood cells. That not accounted for was presumed to be stored in the tissues. In normal subjects the amount absorbed was small (10 to 20 per cent) and the amount not accounted for was usually within the range of experimental error. In chronic hypochromic anemia much larger amounts were absorbed, and the bulk was quickly utilized. In cases of refractory anemia, however, the amount absorbed was often significantly although not grossly larger than the small amount appearing in the hemoglobin. This was also true in one patient with hemochromatosis, who absorbed 20 per cent of the dose but utilized only 2 per cent. It seems, therefore, that in some pathologic states abnormal stores of iron may accumulate from excessive absorption because of an ineffective mucosal block.

After transfusions of blood the iron in the hemoglobin is liberated when the cells eventually disintegrate, and what is not utilized immediately is stored as ferritin. When the cells become saturated with ferritin, additional iron appears as hemosiderin, which gives a positive prussian blue reaction. Hemosiderin appears first in the Kupffer cells and other reticuloendothelial

[1] Dubach, R., Callender, S. T. E., and Moore, C. V.: Studies in iron transportation and metabolism. VI. Absorption of radioactive iron in patients with fever and with anemias of varied etiology, Blood **3**: 526–540, 1948.

[2] Granick, S.: Iron metabolism and hemochromatosis, Bull. New York Acad. Med. **25**: 403–428, 1949.

cells, only later in the parenchymal cells of the liver and other tissues, contrary to what is believed to occur in hemochromatosis. When many transfusions are given and no notable bleeding has occurred, very large amounts accumulate, and the cells may become as distended with granules as in hemochromatosis. Many such cases (at least 40 [3]) have been reported, chiefly pernicious anemia (before liver preparations), other types of refractory anemia and chronic leukemia.

When radioiron is injected intravenously in relatively small doses (Finch et al.[4]), it is removed from the circulation in a few hours, much of it in the liver where it is stored as ferritin. In hypochromic anemia this is quickly mobilized, and it can be detected in circulating red cells within 24 hours. The bulk of the radioiron is so utilized, a large part within two to three days. In refractory anemia and diseases with depressed function of the marrow, increasing the supply of iron does not stimulate the production of hemoglobin, and but little radioiron appears in the circulating cells.

Little is known regarding the late results of the parenteral administration of large doses of iron in man, since the preparations hitherto available caused prohibitively severe toxic reactions. More recently, however, Nissim et al.[5] have perfected a preparation of ferric hydroxide combined with sucrose which is highly effective therapeutically and is virtually nontoxic intravenously in doses up to 200 mg. Their results have been confirmed both in Great Britain and in this country, notably by Brown et al.[3] and by Holly.[6] Such preparations promise to be of practical value in selected cases of hypochromic anemia. If this preparation is given in large amounts to cases of refractory anemia, however, as is likely to be the case, it will merely overload the tissue cells and almost certainly cause hemosiderosis. This is indicated by the experiments of, among others, Polson [7] in rabbits, of Chappel [8] in mice and rats and of Brown et al.[3] in dogs, and by one observation of Holly of the liver of a patient examined by biopsy two months after the administration of about 1.4 gm. of iron. Although the parenchymal cells of the liver and some other tissues of these animals were loaded with hemosiderin, none showed cirrhosis or fibrosis of the liver or pancreas, and the dogs remained clinically healthy during a period of observation of 15 months. The absence of fibrosis might be due, however, to the relatively short duration of the experiment as compared with the decades required for the development of hemochromatosis in man.

[3] Brown, E. B., Moore, C. V. et al.: Saccharated iron oxide intravenously in hypochromic anemia, J. A. M. A. **144**: 1084–1089, 1950.

[4] Finch, C. A., et al.: Utilization of intravenous radioactive iron, Blood **4**: 905–927, 1949.

[5] Nissim, J. A.: Intravenous administration of iron, Lancet **2**: 49–51, 1947.
Nissim, J. A., and Robson, J. M.: Intravenous treatment of anaemia with an iron-sucrose preparation, Lancet **1**: 326–327, 1949.

[6] Holly, R. G.: Intravenous iron: Evaluation and use of saccharated iron oxide in iron deficiency states in obstetrics and gynecology, Blood **6**: 1159–1172, 1951.

[7] Polson, C. J.: The failure of prolonged administration of iron to cause haemochromatosis, Brit. J. Exper. Path. **14**: 73, 1933.

[8] Cappell, D. F.: The late results of intravenous injection of colloidal iron, J. Path. and Bact. **33**: 175, 1930.

The crucial point as to the potential danger of such treatment is whether or not the hemosiderin itself is directly injurious to the tissues and is the exciting cause of the cirrhosis and diabetes. Little help in determining this has been obtained from a study of hemochromatosis. The diagnosis has rarely been made until the terminal stages when the damage has already been done. That hemosiderin is directly harmful to the tissues is plausible and is commonly believed, yet in hemochromatosis there is no close correlation between the amount of hemosiderin in a tissue and the degree of fibrosis. In certain tissues such as the chief cells of the stomach, the cells may be regularly stuffed with granules, yet show no detectable anatomical or functional alteration. In the pancreas, on the other hand, there may be marked fibrosis with severe diabetes, yet relatively little pigmentation. Neither malnutrition, a history of an ill balanced diet nor anemia is encountered in hemochromatosis except as an incidental complication. The most plausible explanation at present seems to be a disproportion between the amount of iron absorbed and that utilized.[1] An average excess of 2 to 3 mg. per day would suffice to produce the stores found in these cases. The lack of an effective mucosal block may be one manifestation of a constitutional metabolic anomaly. The amount of copper and of certain other minerals stored is also increased. The occasional familial occurrence of the disease likewise gives some support to this view.

Extensive siderosis, often accompanied by cirrhosis, has been described by Gillman et al.[9] in malnourished South African negroes with pellagra who have subsisted on a diet largely of corn meal, and they have produced a similar condition experimentally by feeding this diet to young rats. There was neither significant anemia nor evidence of increased hemolysis in these cases and none had received transfusions. The Gillmans apply the term cytosiderosis to this condition, since they believe the pigment does not come from hemoglobin. They made a careful study by serial biopsies of the liver in many subjects and by examination of autopsy material from victims of accidental death. As the disease is common in this economic group, such material was abundant. They described three types or stages of hepatic lesions: (1) Fatty infiltration, without an increase of iron; (2) small to large amounts of cytosiderin (hemosiderin) confined to the parenchymal cells; and (3) similar parenchymal siderosis with pigment also in the portal tracts and Kupffer cells and histiocytes. Cirrhosis may be present in any one of these types. It was most frequent and usually most marked in the third type, with lesions closely resembling those in hemochromatosis, but there was no good correlation between the degree of fibrosis and cirrhosis and either the amount of pigment or the age of the patient and the presumed duration of the disease.

[9] Gillman, J., et al.: A comparison of chemical and histological estimations of the iron and copper content of the livers of Africans in relation to the pathogenesis of cytosiderosis and cirrhosis (haemochromatosis), South African J. M. Sc. **10**: 109–136, 1945.

Gillman, J., and Gillman, T.: The pathogenesis of cytosiderosis (haemochromatosis) as evidenced in malnourished Africans, Gastroenterology **8**: 19–23, 1947.

In these cases, the hemosiderin appears first in parenchymal cells and only later in the reticuloendothelial cells, in contrast to what happens in transfusion siderosis. They advance evidence to show a disturbance of intracellular metabolism, describe the appearance of fluorescent substances in the affected cells, and believe that the iron is derived from the breakdown of oxidative ferments and other cytoplasmic constituents, particularly the mitochondria, and accumulates because, when so liberated, for some unknown reason the iron can not again be utilized. They doubt whether the cytosiderin is even a contributing factor in producing cirrhosis.

Others have suggested that excessive absorption of iron occurs because of a deficiency of phosphorus in the diet of these Africans, and that the relatively abundant iron available comes from their cooking utensils.

Conclusions as to the etiology of hemochromatosis or the harmlessness of the hemosiderin granules can be drawn from these observations only with great caution, since the etiologic factors, the multiple dietary deficiencies producing cytosiderosis, are not operative in this country. Although the lesions in the terminal stage are similar, the pathogenesis may be quite different.

A study of the reported cases of transfusion siderosis (reviewed by Schwartz and Blumenthal [10] and more recently and sketchily by Brown et al.[3]) reveals both similarities to and differences from hemochromatosis, and it probably represents more nearly what might be anticipated from the reckless administration of iron. The quantity of hemosiderin found has varied greatly, depending primarily upon the number of transfusions and the duration of the illness. In some the amount was huge and quite comparable to that in hemochromatosis. In some cases the excess of iron could be accounted for by the blood administered, but in many it has been much greater, even 10 to 20 times as great (Chesner [11]), and excessive absorption must also be assumed, as in hemochromatosis.

In the more marked cases some degree of fibrosis of the liver and of siderosis and fibrosis of the pancreas and other organs is usual. Typical portal cirrhosis of marked degree in uncommon, however, and diabetes is rare. Marked pigmentation of the skin is much less common than in hemochromatosis, but it does occur, and in Kark's patient [12] who had received 290 transfusions in 9 years the pigmentation also involved the mucous membranes and the teeth. These differences, however, might be due to the shorter duration of the illness. As in hemochromatosis, there is no close correlation between the degree of siderosis and the fibrosis. Furthermore, other factors associated with the severe underlying disease, such as anoxia and intercurrent infection, undoubtedly contribute to the tissue injury.

[10] Schwartz, S. O., and Blumenthal, S. A.: Exogenous hemochromatosis resulting from blood transfusions, Blood **3**: 617-640, 1948.

[11] Chesner, C.: Hemochromatosis. Review of literature and presentation of a case without pigmentation or diabetes, J. Lab. and Clin. Med. **31**: 1029-1936, 1946.

[12] Kark, R. M.: Two cases of aplastic anaemia. One with secondary haemochromatosis following 290 transfusions in nine years, and the other with secondary carcinoma of the stomach, Guy's Hosp. Rep. **87**: 343-353, 1937.

That hemosiderosis may make an individual vulnerable is suggested by the patient of Humphries and Southworth,[13] a woman who was cured of a severe refractory anemia by removal of a mediastinal tumor after receiving many transfusions for 22 months. After a year of apparently normal health, she incurred an infection of the thigh which failed to heal and after a few weeks became severely ill with jaundice and ascites and died apparently of hepatic insufficiency. The autopsy, inadequately reported, showed enlargement of the liver and extensive hemosiderosis of the liver, pancreas and other organs, which was interpreted as hemochromatosis.

That hemosiderin is directly harmful is strongly suggested by the observations of Davis et al.[14] in three cases of hemochromatosis treated by numerous frequent venesections, with removal of from 4 to 7 pints per month for periods up to two years. The plasma was reinjected to avoid depleting the plasma proteins. They noted a very rapid restoration of the red cell count, indicating that the hemosiderin could be utilized. The patients were all subjectively improved. There was improvement in hepatic function and a "return toward normal" of the carbohydrate metabolism. Serial biopsies of the liver showed diminution of the amount of pigment and "improvement in the appearance of the cirrhosis." Confirmation of this on an adequate scale would brand the hemosiderin as definitely harmful.

One may conclude that even marked degrees of siderosis may cause little or no immediate disturbance of function of the cells affected. It seems probable that the hemosiderosis is not the sole cause and may not be the major cause of the fibrosis, which undoubtedly can secondarily injure the secreting cells. That the siderosis may be an important aggravating factor has not been disproved, however, and there is considerable evidence that it is eventually harmful. Overloading the tissues with iron, therefore, incurs a potential danger which should be avoided. Iron should not be given intravenously to patients with refractory anemia because they are refractory on oral administration, but only to those who have a hypochromic anemia with iron deficiency. It should not be given in a quantity materially greater than is needed to replace this deficiency, as calculated from the amount of hemoglobin and the probable blood volume. With this precaution, intravenous administration of iron should be valuable in a small selected group in whom iron orally administered is disturbing or poorly absorbed, and in the later stage of pregnancy, when rapid replenishment of the iron stores is important.

P. W. C.

[13] Humphries, G. H., and Southworth, H.: Aplastic anemia terminated by removal of a mediastinal tumor, Am. J. M. Sc. **210**: 501–510, 1945.

[14] Davis, W. D., Jr., and Arrowsmith, W. R.: The effect of repeated bleeding in hemochromatosis, J. Lab. and Clin. Med. **36**: 814–815, 1950. (Abstract.)

REVIEWS

Les Stimulines Hypophysaires. By André Lemaire, Florian Delbarre and J. P. Michard. 174 pages; 17 × 25 cm. Masson and Cie, Paris. 1951. Price, 750 fr.

An admirably concise and accurate account of our present knowledge concerning the hypophysis. The treatment is synoptic but surprisingly thorough and complete with all of the essential facts about the hypophysis included and the current theories regarding hypophyseal function well presented. In short it is the sort of thing for which the French are justly famous and which, when they do it well, they do with consummate skill. The physiological approach is used throughout and the development is logical and clear. The book is highly recommended to all who want to broaden their understanding of how this vital part of the endocrine system works. There are chapters on the rôle of the hypophysis in pathology, the rôle of the hypophyseal hormones in hematopoiesis, their relation to carcinogenesis and their place in therapy. A well selected bibliography of over 300 titles includes most of the significant papers which have appeared in the field during the past 20 years. The few diagrams in the text are excellent and clearly and simply show the complex web of relationships which exists between the hypophysis and the other glands of internal secretion. There is no index.

The various chapters of the book cover methods for hypophysectomy, the effects of hypophysectomy, the rôle of the individual hypophyseal hormones, methods for their assay and isolation and an account of their chemical properties. Included in this last is an excellent summary of the interesting chemical differences between LH in swine and sheep. A chapter on antihormones is also included. The discussion of the factors controlling the rate of secretion and release of the hypophyseal hormones is particularly good and is presented from the viewpoint of the clinician who is interested in the possible application of this knowledge to practice. Certainly no one today should use these compounds without some realization of how their presence or absence affects the activity of other glands of internal secretion.

One of the best sections of the book is a review of the relationship between the hypophysis and the hypothalamus and a consideration of the means whereby the hypothalamus can influence the hypophysis. Increasing recognition is being given to the fact that the hypothalamus not only controls the posterior lobe but may very well in some animals and under certain conditions influence the anterior lobe besides, particularly in regard to the release of ACTH and possibly certain of the gonadotrophic hormones, particularly LH. The discussion makes it quite obvious that environmental factors such as light, temperature and sexual excitement can influence the level of hypophyseal hormones in the blood. Obviously the spatial limitations of the book impose a dogmatic approach and on occasion some of the statements made appear rather sweeping in their implications. The hypothesis that the release of ACTH depends upon the action of adrenalin upon certain hypothalamic nuclei seems to be accepted without question. The so-called negative feed back principle is not neglected but perhaps it deserves more emphasis particularly in respect to the relationship between the thyroid and the hypophysis. The authors are quite correct in pointing out that we know nothing about how the secretion of growth hormones is regulated in spite of the fact that their metabolic rôle is becoming increasingly important. All in all the book is a welcome and useful addition to the ever growing and expanding body of endocrinological literature.

D. C. S.

The Approach to Cardiology. By CRIGHTON BRAMWELL, M.A., M.D., F.R.C.P. 122 pages; 25 × 16 cm. Oxford University Press, New York. 1951. Price, $3.75.

The author, who is Professor of Cardiology in the University of Manchester in England, is perhaps best known to American readers for having joined auctorial hands across the sea with Dr. John T. King in the coauthorship of *Principles and Practice of Cardiology*.

For the past several years, in order to bridge the uncomfortable gap between preclinical and clinical studies, a series of 70 lectures has been given to students at Manchester during their first six months in the wards. This book is based on some of the author's lectures that formed part of this series. It is therefore written primarily for medical students and is designed to illustrate the application of knowledge gained in the laboratory to the study of patients in the wards.

The subjects covered are as follows: The Clinical Approach, Cardiac Enlargement, Valvular Lesions, The Pulse, Cardiac Arrhythmias, Heart Failure, The Aetiology of Heart Disease. There is no doubt that the author admirably achieves his purpose "to illustrate some of the fundamental general principles of cardiology in relation to the pre-clinical sciences." The text is lucid and simple, and amply and excellently illustrated. The section on the pulse contains much that is important yet not common knowledge on the dynamics of the pulse wave and the blood pressure.

The important subject of triple rhythms is not as well discussed or illustrated as most of the topics, and this section may well lead to confusion in the student reader's mind. One is disappointed to find circus movement again accepted without question in the account of the arrhythmias, when its existence has been so emphatically disputed and even disproved in recent years. And perhaps the concepts of high and low output failure might with profit have been more fully developed in the chapter devoted to failure.

Against a background of general excellence these criticisms are minor, and no student could help but benefit from carefully reading and rereading the contents of this brief introduction to clinical cardiology.

H. J. L. M.

Children's Radiographic Technic. By FORREST E. SHURTLEFF, R. T., Children's Medical Center, Boston, Massachusetts. 80 pages; 18 × 26.5 cm. Lea & Febiger, Philadelphia. 1951. Price, $3.75.

This book is briefly written in four chapters covering equipment and accessories, children's radiographic positions, special radiographic procedures and technic charts. It is written as a supplement to the many texts on radiographic technic and should not be used as a replacement for these.

The material presented is of value mainly to pediatricians and physicians who have had no special training in radiology and who do their own radiographic work. The procedures outlined differ only slightly from those used in most general hospitals and are of little value to the radiologist. Methods of handling uncooperative children for the various procedures are discussed, but in general they consist of having adequate personnel for immobilization.

From the radiologist's standpoint, the most valuable portion of the book is the section containing the tables of technical factors, which have been developed by the author from his wide experience in pediatric radiographic technic.

J. M. D.

Gynaecological Endocrinology for the Practitioner. 2nd Ed. By P. M. F. BISHOP, D.M. (Oxon.) 132 pages; 19 × 12.5 cm. The Williams and Wilkins Company, Baltimore. 1951. Price, $3.00.

This handbook should serve as a ready reference for the general practitioner. It brings to date the most acceptable endocrine interpretation of gynecological disorders.

The chapter on steroid chemistry is of minimal interest to those for whom the book is designed. This space might better be devoted to more elaborate discussion of the menopause and its therapy.

The therapeutic schedules outlined in the appendix are useful as a guide, but are not applicable in the management of all individual patients.

The chapter on infertility, though well written, does not accurately belong in a text whose theme is endocrinology.

W. K. D.

BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Adrenal Cortex: Transactions of the Second Conference, November 16–17, 1950, New York, N. Y. Edited by ELAINE P. RALLI, Department of Medicine, College of Medicine, New York University, New York, N. Y. 209 pages; 23.5 × 15.5 cm. 1951. Sponsored by Josiah Macy, Jr. Foundation, New York. Price, $3.00.

Antibiotic Therapy. By HENRY WELCH, Ph.D., Director, Division of Antibiotics, Food and Drug Administration, Federal Security Agency of the United States Government, and CHARLES N. LEWIS, M.D., Medical Officer, Division of Antibiotics, Food and Drug Administration, Federal Security Agency of the United States Government; foreword by CHESTER S. KEEFER, M.D., Wade Professor of Medicine, Boston University School of Medicine, etc. 562 pages; 22 × 15 cm. 1951. The Arundel Press, Inc., Washington, D. C. Price, $10.00.

Cardiac Pain. By SEYMOUR H. RINZLER, M.D., F.A.C.P., Adjunct in Medicine and Cardiovascular Research Unit, Beth Israel Hospital, etc. 139 pages; 22.5 × 14.5 cm. 1951. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $3.75.

Cardiolipin Antigens: Preparation and Chemical and Serological Control. By MARY C. PANGBORN, Ph.D., F. MALTANER, Ph.D., V. N. TOMPKINS, M.D., T. BEECHER, M.D., W. R. THOMPSON, Ph.D., and MARY ROSE FLYNN, Division of Laboratories and Research, New York State Department of Health, Albany, N. Y. 63 pages; 24 × 16 cm. (paperbound). 1951. World Health Organization, Geneva; Agents for U.S.A.: Columbia University Press, International Documents Service, New York, N. Y. Price, $1.00.

Conference on Problems of Aging: Transactions of the Thirteenth Conference, February 5–6, 1951, New York, N. Y. Edited by NATHAN W. SHOCK, Chief, Section on Gerontology, National Heart Institute, National Institutes of Health and The Baltimore City Hospitals, Baltimore, Md. 194 pages; 23.5 × 15.5 cm. 1951. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $4.00.

A Course in Practical Therapeutics. 2nd Ed. By MARTIN EMIL REHFUSS, M.D., F.A.C.P., Professor of Clinical Medicine and Sutherland M. Prevost Lecturer in Therapeutics, The Jefferson Medical College, Philadelphia, etc., and ALISON HOWE PRICE, A.B., M.D., Associate Professor of Medicine, The Jefferson Medical College, Philadelphia, etc. 938 pages; 29 × 22.5 cm. 1951. The Williams & Wilkins Company, Baltimore. Price, $15.00.

Differentialdiagnostische Symptomatologie. By PROFESSOR DR. MED. WERNER CATEL. 640 pages; 24.5 × 17.5 cm. 1951. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 69.–

Disorders of the Heart and Circulation. Edited by ROBERT L. LEVY, M.D., Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, etc. 944 pages; 25.5 × 18.5 cm. 1951. Thomas Nelson & Sons, New York; available from The Williams & Wilkins Company, Baltimore. Price, $12.00.

Expert Committee on the International Pharmacopoeia: Report on the Eighth Session, Geneva, 19–28 April 1951—World Health Organization Technical Report Series No. 43. 35 pages; 24 × 16 cm. (paper-bound). 1951. World Health Organization, Geneva; Agents for U.S.A.: Columbia University Press, International Documents Service, New York, N. Y. Price, 25¢.

Factors Regulating Blood Pressure: Transactions of the Fifth Conference, February 15 and 16, 1951, New York, New York. Edited by BENJAMIN W. ZWEIFACH and EPHRAIM SHORR, Department of Medicine, Cornell University Medical College, New York, New York. 238 pages; 23.5 × 15.5 cm. 1951. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $3.75.

Formulary and Therapeutic Guide. R. GORDON DOUGLAS, Chairman; DONALD A. CLARKE, Secretary; NORMAN BAKER, HENRY BARNETT, McKEEN CATTELL, HERBERT CONWAY, CARY EGGLESTON, AUGUST GROESCHEL, VASSAR JOHNSON, VERNON KNIGHT and ADE MILHORAT. 355 pages; 19.5 × 12.5 cm. 1951. Appleton-Century-Crofts, Inc., New York. Price, $3.00.

Joint FAO/WHO Expert Committee on Nutrition: Report on the Second Session, Rome, 10–17 April 1951—World Health Organization Technical Report Series No. 44. 64 pages; 24 × 16 cm. (paper-bound). 1951. World Health Organization, Geneva; Agents in U.S.A.: Columbia University Press, International Documents Service, New York, N. Y. Price, 40¢.

Kreislaufuntersuchungen am Menschen mit Fortlaufend Registrierenden Methoden. By K. MATTHES. 326 pages; 25 × 17.5 cm. 1951. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 48.–

Liver Injury: Transactions of the Ninth Conference, April 27 and 28, 1950, New York, New York. Edited by F. W. HOFFBAUER, M.D., Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota. 232 pages; 23.5 × 15.5 cm. 1951. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y. Price, $3.00.

Medical Milestones. By HENRY J. L. MARRIOTT, M.D.; Foreword by SIR ALEXANDER FLEMING. 293 pages; 22.5 × 15 cm. 1952. The Williams & Wilkins Company, Baltimore. Price, $3.50.

Modern Electrocardiography. Volume I: The P-Q-R-S-T-U Complex. By EUGENE LELESCHKIN, M. D., Assistant Professor of Experimental Medicine, University of Vermont College of Medicine; Foreword by FRANK N. WILSON, M.D., Professor of Medicine, University of Michigan Medical School. 598 pages; 26 × 18 cm. 1951. The Williams & Wilkins Company, Baltimore. Price, $12.00.

Nerve Impulse: Transactions of the Second Conference, March 1–2, 1951, New York, N. Y. Edited by DAVID NACHMANSOHN, M.D., Department of Neurology, College of Physicians and Surgeons, Columbia University. 204 pages; 23.5 × 15.5 cm. 1951. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $3.50.

Penicillin Decade—1941–1951: Sensitizations and Toxicities. By LAWRENCE WELD SMITH, M.D., Medical Director, Commercial Solvents Corporation, and ANN DOLAN WALKER, R.N., Former editor, "Trained Nurse and Hospital Review." 122 pages; 22 × 14.5 cm. (leather-bound). 1951. Arundel Press, Inc., Washington, D. C. Price, $2.50.

Pharmacopoea Internationalis. Volume I. 406 pages; 24.5 × 16.5 cm. 1951. World Health Organization, Geneva; Agents for U.S.A.: Columbia University Press, International Documents Service, New York. Price, $5.00.

Prevention and Treatment of Severe Malnutrition in Times of Disaster: Report approved by the Joint FAO/WHO Expert Committee on Nutrition and presented to the Fourth World Health Assembly—World Health Organization Technical Report Series No. 45. 56 pages; 24 × 16 cm. (paper-bound). 1951. World Health Organization, Geneva; Agents for U.S.A.: Columbia University Press, International Documents Service, New York. Price, 35¢.

Renal Function: Transactions of the Second Conference, October 19–20, 1950, New York, N. Y. Edited by STANLEY E. BRADLEY, Department of Medicine, College of Physicians and Surgeons, Columbia University. 178 pages; 23.5 × 15.5 cm. 1951. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $3.00.

Report of the Medical Research Council for the Years 1948–1950. Presented by the Lord President of the Council to Parliament by Command of His Majesty, July 1951. 247 pages; 24.5 × 15 cm. (paper-bound). His Majesty's Stationery Office, London. Price, 6s 6d net.

Untoward Reactions of Cortisone and ACTH. By VINCENT J. DERBES, M.D., F.A.C.P., Associate Professor of Medicine, Tulane University of Louisiana School of Medicine, etc., and THOMAS E. WEISS, M.D., Instructor in Medicine, Tulane University of Louisiana School of Medicine, etc. 77 pages; 22.5 × 14.5 cm. (limp leather binding). 1951. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $2.25.

COLLEGE NEWS NOTES

Nominations for A.C.P. Elective Offices, 1952–53

In accordance with provisions of the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1952–1953, are herewith announced to the Fellows and Masters of the College:

President-Elect.....LeRoy H. Sloan, Chicago, Ill.
First Vice President.....Walter B. Martin, Norfolk, Va.
Second Vice President.....Charles F. Moffatt, Montreal, Que.
Third Vice President.....Paul F. Whitaker, Kinston, N. C.

Regular elections will take place at the 1952 Annual Session at Cleveland, Ohio, April 24, 1952, the date of the Annual Business Meeting at the Municipal Auditorium, general headquarters.

The election of nominees shall be by the Fellows and Masters of the College. The above nominations do not preclude other nominations made from the floor at the Business Meeting.

Nominations of members of the Board of Regents and Board of Governors will be presented at the Business Meeting, as provided in the By-Laws.

Respectfully submitted,
A. B. Brower, Dayton, Ohio
Chairman, Committee on Nominations

A.C.P. Postgraduate Courses, Spring of 1952

Course 1. GASTRO-ENTEROLOGY: University of California Medical School and Stanford University School of Medicine, San Francisco, Calif.; Theodore L. Althausen, M.D., F.A.C.P., and Dwight L. Wilbur, M.D., F.A.C.P., Directors; one week, February 25-March 1, 1952.

Course 2. CURRENT CONCEPTS OF ALLERGY AND ASSOCIATED DISORDERS: Washington University School of Medicine, St. Louis, Mo.; Harry L. Alexander, M.D., F.A.C.P., Director; one week, March 3–7, 1952.

Course 3. DISEASES OF THE BLOOD VESSELS: Cornell University Medical College and New York Hospital, New York, N. Y.; Irving S. Wright, M.D., F.A.C.P., Director; one week, March 10–15, 1952.

Course 4. CLINICAL MEDICINE FROM THE HEMATOLOGICAL VIEWPOINT: Ohio State University College of Medicine, Columbus, Ohio; Charles A. Doan, M.D., F.A.C.P., Director; one week, March 17–21, 1952.

Course 5. INTERNAL MEDICINE: University of Michigan Medical School, Ann Arbor, Mich.; Cyrus C. Sturgis, M.D., F.A.C.P., Director; one week, April 14–18, 1952.

Course 6. ELECTROCARDIOGRAPHY—BASIC PRINCIPLES AND INTERPRETATION: Massachusetts General Hospital, Boston, Mass.; Conger Williams, M.D., one week, May 12–17, 1952.

This course is already registered to full capacity and no additional applications can be honored.

Course 7. TRENDS AND NEWER DEVELOPMENTS IN INTERNAL MEDICINE: Hahnemann Medical College and Hospital of Philadelphia, Pa.; Charles L. Brown, M.D., F.A.C.P., Director; one week, May 12–16, 1952.

Course 8. PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE: University of Toronto Faculty of Medicine, Toronto, Ont.; Ray F. Farquharson, M.D., F.A.C.P., Director; one week, June 2–7, 1952.

For course outlines, detailed bulletins, and registration forms address E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia, 4, Pa.

FORTHCOMING A.C.P. REGIONAL MEETINGS

Territory	City	Date	A.C.P. Governor	Special Guest(s)
Nebraska	Lincoln	February 23, 1952	J. D. McCarthy, M.D.	LeRoy H. Sloan, M.D., Chicago, Regent, A.C.P.
Virginia	Charlottesville	February 28, 1952	Charles M. Caravati, M.D.	Pending
Maryland District of Columbia and Delaware	Baltimore	March 1, 1952	R. Carmichael Tilghman, M.D.	M. C. Pincoffs, M.D., Baltimore, President, A.C.P.
Kansas	Emporia	March 21, 1952	William C. Menninger, M.D.	M. C. Pincoffs, M.D., Baltimore, President, A.C.P.
North Dakota	Grand Forks	September 13, 1952	Robert B. Radl, M.D.	Pending
New Jersey	Newark	November 5, 1952	Edward C. Klein, Jr., M.D.	T. Grier Miller, M.D., Philadelphia, President, A.C.P.
Mid-West States	Chicago	November 22, 1952	Howard Wakefield, M.D.	T. Grier Miller, M.D., Philadelphia, President, A.C.P. E. R. Loveland, Executive Secretary

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NEW LIFE MEMBERS

The College is gratified to announce that the following Fellows have become Life Members of the American College of Physicians since the publication of the last issue of this journal:

Dr. Lee E. Sutton, Jr., Richmond, Va.
Dr. Theodore Z. Polley, Joliet, Ill.
Dr. Robert van Zandt Bucklin, Saginaw, Mich.
Dr. Edward H. Robitzek, Staten Island, N. Y.
Dr. Donald A. Dupler, Philadelphia, Pa.
Dr. Aaron Feder, Jackson Heights, N. Y.
Dr. Ralph T. Warburton, North Canton, Ohio
Dr. Joseph McMilton Wilson, Dayton, Ohio
Dr. Martin H. Collier, Blackwood, N. J.

Gifts to the College Library of Publications by Members

Dr. Emmet F. Horine, F.A.C.P., Louisville, Ky., has donated two books of his editorship, autographed by him, to the American College of Physicians. Each is a specimen of the printers art, beautifully printed on antique finish paper and bound in Vellum de Lux cloth. Each book has been published in a limited edition.

"An Inaugural Discourse on Medical Education by Daniel Drake, M.D." No. 168.

"Pioneer Life in Kentucky, 1785–1800, by Daniel Drake, M.D." No. 148.

Additionally, Dr. Horine sent several reprints of his other publications for the College Archives.

Dr. Noble Pierce Sherwood, F.A.C.P., Lawrence, Kans., has presented the College Library with an autographed copy of his book, "Immunology," which was published by the C. V. Mosby Company.

The College Library of Publications by Members is maintained at College headquarters. Members frequently present copies of their books to the College and thus the Library has become a living memorial to the member-authors.

American Board of Internal Medicine Examinations

The American Board of Internal Medicine has scheduled the following oral examinations for 1952: Cleveland, Ohio, April 17–19; Chicago, Ill., June 5–7; San Francisco, Calif., September or October; New York, N. Y., November or December.

The written examination will be held October 20 in various centers and overseas. The closing date for acceptance of applications for the written examinations will be May 1, 1952.

Milwaukee Health Department Seeking Physicians

Dr. Virginia Downes, Superintendent, Bureau of Maternal and Child Care, Health Department of the City of Milwaukee, Milwaukee 2, Wis., has announced vacancies for the following physicians:

1. Public Health Physician I at a beginning salary of $7,375.00 (if certified in preventive medicine or in pediatrics, $7,975.00). The qualifications for this position are M.P.H. degree or two years residency in pediatrics.
2. Physician II at a beginning salary of $6,535.00. Must be interested in public health or in pediatrics; no special training requirements are made other than eligibility for licensure in Wisconsin; position requires accepting responsibility for an area about one-twelfth the size of Milwaukee which includes a population of fifty thousand people.
3. Public Health Physician II at a beginning salary of $8,575.00; this position in the field of school health and requires experience in public health, a degree in public health, and an interest or experience in school health.

Courses in Diseases of the Heart and Vascular System

A series of postgraduate courses in the field of cardiology, electrocardiography, peripheral vascular diseases, etc., is scheduled regularly as a part of the educational program of the New York University Post-Graduate Medical School and Columbia University. They are under the Fellowship Program of the New York State Department of Health, New York City Department of Health and the Medical Society

of the State of New York. Several of the Directors are Fellows of the American College of Physicians.

Fellowships for the courses are limited to physicians living in the State of New York. Application blanks and detailed information may be obtained from the New York State Department of Health, 39 Columbia St., Albany 7, N. Y.

The Joint Commission on Accreditation of Hospitals

The Canadian Medical Association has joined the Joint Commission on Accreditation of Hospitals, in addition to the American Medical Association, The American College of Physicians, The American College of Surgeons and the American Hospital Association. The Canadian Medical Association will have two representatives on the Commission, namely Dr. E. K. Lyon of Leamington, Ontario, with Dr. A. D. Kelly, Deputy General Secretary of the Canadian Medical Association, acting as alternate.

At a meeting of the Joint Commission at Chicago on December 15, 1951, Dr. Gunnar Gunderson, a representative of the American Medical Association was made Chairman of the Commission, Dr. LeRoy H. Sloan, a representative of the American College of Physicians, was named Vice Chairman and Mr. Stuart K. Hummel of Joliet, Illinois, was elected Treasurer.

"Doctor-in-Training" Program at University of Pennsylvania

To implement a new "Doctor-in-Training" program instituted at the University of Pennsylvania as an addition to the curricula of its School of Medicine, the Commonwealth Fund of New York has awarded a grant amounting to $22,500 annually for two years.

Under the "Doctor-in-Training" plan, students in the first year of their medical education and extending until graduation, are assigned to individual families in Philadelphia area homes, where they serve as family health advisers with close faculty supervision. The University of Pennsylvania School of Medicine is said to be the first American institution of medical learning to initiate such a plan extending through four years of medical education.

Organized over two years ago by Dr. John McK. Mitchell, Dean of the School of Medicine, the new departure in medical education was devised to provide an opportunity for medical students to assume gradually increasing responsibility for the medical and related problems of families assigned to the students and followed by them in the clinic, hospital and home throughout their four years in medical school.

The student-doctor, who is designated as a family health adviser, helps in coordinating the medical care of a given family. At least once a month, he visits the family to which he is assigned. All environmental factors are taken into consideration. Emotional problems as well as physical difficulties are studied at close range. Where and when circumstances indicate the need of professional services, the student-doctor reports these facts back to his faculty advisers. At no time does the doctor-in-training take over responsibility for medical treatment.

Dr. Bernard Sternberg, F.A.C.P., Brooklyn, N. Y., was recently appointed Clinical Instructor in Medicine by the State University Medical Center at New York City, College of Medicine.

Dr. James Campbell (Associate), formerly of Chicago, has been named Dean and Professor of Medicine at the Albany Medical College, Albany, N. Y.

Dr. Francis G. Blake, F.A.C.P., wartime adviser to President Roosevelt on epidemic disease problems, and former Dean of the Yale University School of Medicine, has been appointed civilian Technical Director of Medical Research in the Office of the Surgeon General, U. S. Army.

Dr. Blake will serve as expert consultant to Colonel John R. Wood, MC, Chairman of the Army Medical Research and Development Board, in the evaluation of current and proposed research projects conducted by Army medical installations and 81 cooperating civilian institutions. He will be responsible for ensuring close coordination between the Army's present $10,079,000 medical research effort and similar programs sponsored by the other Armed Forces and other Federal agencies.

Walter Reed Society Organized

Dr. Max Sadove, Head of the Department of Anesthesiology at the University of Illinois, was elected Organizing President of the Walter Reed Society at the first official meeting of the group held in Los Angeles, Calif., at the close of the American Medical Association meetings.

The society which is sponsored by the National Society for Medical Research is comprised of those who have served as "human guinea pigs" in medical research or experimentation under the direction of a qualified scientist. It is named in honor of Dr. Walter Reed who risked his life in the fight against Yellow Fever and who first dramatized the use of the human volunteer in experimental medicine.

Dr. Sadove has frequently been a "guinea pig" and has just recently conducted some dramatic experiments with 50 volunteers at the University of Illinois. These experiments had to do with artificial respiration studies conducted at the request of the Defense Department. As a result of these experiments, a method of artificial respiration proved to be the most satisfactory from every standpoint has been officially adopted by the Red Cross and all military units.

St. Mary's Hospital of Rochester, N. Y., has affiliated with Georgetown University College of Medicine, of Washington, to augment its teaching facilities. Fulltime men from Georgetown University will visit St. Mary's Hospital monthly for periods of four to five days, and internes and residents will be rotated for brief periods through the Georgetown center. The plan also provides for visits of St. Mary's attending staff to Georgetown center for short periods for special instruction and observation. This is a new venture in the field of postgraduate education and is under the direction of Dr. Harold Jeghers, F.A.C.P., Professor of Medicine at Georgetown. Dr. Leo F. LaPalm, F.A.C.P., is Chief of Staff of St. Mary's Hospital.

Dr. Leon Hugh Warren, F.A.C.P., has removed from private practice in Philadelphia to accept an appointment with the National Research Council in Washington, D. C.

The North Carolina Regional Meeting of the American College of Physicians was held at Durham, December 6, 1951, under the Governorship of Dr. Elbert L. Persons, F.A.C.P. Dr. Verne S. Caviness, F.A.C.P., Raleigh, was Chairman of the Program Committee and Dr. James P. Hendrix, F.A.C.P., Durham, was Chairman of the Committee on Arrangements. Among guests in attendance were Dr. Charles M. Caravati, F.A.C.P., College Governor for Virginia, and Dr. Cyrus C. Sturgis, F.A.C.P. Ann Arbor, Mich., a Regent of the College. Dr. Sturgis delivered the banquet address and discussed a number of the activities of the College at the national

and international levels. In attendance were 78 members of the College and 38 non-members; a total of 116, an exceptionally fine showing.

Among the Honor Guests at the Spring Clinical Conference of the Dallas Southern Clinical Society to be held March 17–20, will be Dr. William B. Castle, F.A.C.P., Boston, Mass., Dr. George C. Griffith, F.A.C.P., Los Angeles, Calif., Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, Pa., and Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.

Dr. George E. Pfahler, F.A.C.P., Philadelphia, Pa., was awarded the Gold Medal of the American College of Radiology at the Annual Meeting of the College in Chicago, February 8. This was the 8th Gold Medal Award in the twenty-nine year history of the College. Dr. Pfahler served as the first President of the American College of Radiology in 1923.

At the Annual Business Meeting of the Omaha Mid-West Clinical Society on November 27, 1951, Dr. J. Harry Murphy, F.A.C.P., Omaha, was installed as President. At the same time, Dr. Friedrich W. Niehaus, F.A.C.P., Omaha, was elected a member of the Executive Committee. Dr. Joseph D. McCarthy, F.A.C.P., College Governor for Nebraska, was carried over in his Office as Counselor.

The Twentieth Annual Assembly of the Society will be held in Omaha, October 27 to 31, 1952.

Dr. James E. McCormack (Associate), New York, N. Y., was recently appointed Associate Dean for Graduate Studies and Assistant Professor of Medicine at Columbia University College of Physicians and Surgeons.

Among guest speakers at the International Medical Assembly of Southwest Texas, held in San Antonio, January 22–24 were Dr. Henry L. Bockus, F.A.C.P., Philadelphia, Pa., "Some Cardiovascular Gastrointestinal Interrelationships"; Dr. H. Marvin Pollard, F.A.C.P., Ann Arbor, Mich., "Management of Upper Gastrointestinal Tract Hemorrhage," and Dr. George F. Lull, F.A.C.P., Chicago, Ill., "What Do I Get for My AMA Dues?"

Captain John Ryer Poppen, MC, U. S. Navy, F.A.C.P., Drexel Hill, Pa., retired from active Navy duty January 1, 1952. Prior to his retirement, Captain Poppen had served as Director of the Navy's newest Aviation Medical Acceleration Laboratory located at the Naval Air Development Center, Johnsville, Bucks County, Pa., since November, 1949.

During his more than 35 years Naval service, Captain Poppen has made many contributions to the field of naval aviation medicine. He was the first U. S. doctor to study the effects of accelerative forces upon pilots and began his research in this field in 1934. Among other achievements, he is credited with developmental work of the pilot ejection seat and the development of the pilot anti-acceleration belt and anti-acceleration suit which enables pilots to withstand greater than normal accelerative stress encountered in high-speed flight.

Dr. Charles L. Harrell, Sr., F.A.C.P., Norfolk, Va., has retired from the practice of medicine to accept a full-time position as Medical Director of the Tidewater

Regional Blood Center of the American Red Cross, with offices at 415 W. York St., Norfolk, Va. He nas retained his position as Civilian Consultant at the U. S. Naval Hospital, and Honorary Consultant to the Norfolk General Hospital. Dr. Harrell is a Life Member of the College.

Dr. Joseph W. Post, F.A.C.P., was installed January 9 as the 91st President of the Philadelphia County Medical Society. Dr. Post succeeds Dr. Louis B. Laplace, F.A.C.P.

Dr. Herbert Pollack, F.A.C.P., is scheduled to visit Japan and Korea as Consultant in Nutrition to the Surgeon General of the Department of the Army.

Dr. W. Barry Wood, Jr., Busch Professor of Medicine, Washington University, served as Physician-in-Chief pro-tempore at the Peter Bent Brigham Hospital during the week beginning January 14, 1952.

Dr. William S. Middleton, F.A.C.P., Dean and Professor of Medicine of the University of Wisconsin, addressed the Academy of Medicine in San Francisco at their dinner meeting on December 8, 1951. The subject of his address was "The Golden Age of Medicine."

Dr. Stacy R. Mettier, F.A.C.P., Professor of Medicine, University of California, and Governor of the College for Northern California, is to be President of the San Francisco Medical Society for the year 1952.

Dr. William J. Kerr, F.A.C.P., Professor and Chairman of the Division of Medicine, University of California School of Medicine, has been on sabbatical leave of absence during 1951 and expects to resume his duties in January, 1952.

OBITUARIES

REAR ADMIRAL CLYDE WINDON BRUNSON

Rear Admiral Clyde W. Brunson, MC, U. S. Navy, District Medical Officer, 13th Naval District, died of a heart attack while en route to Washington, D. C., on December 19, 1951.

Admiral Brunson was born May 23, 1895, in Pascagoula, Miss. He attended the University of Mississippi at Oxford, where he received his B.S. degree in 1915; and the University of Pennsylvania School of Medicine, where he received the degree of Doctor of Medicine in 1918.

He was a member of the U. S. Army Reserve from October, 1917, until June, 1918, when he was commissioned in the Medical Corps of the U. S. Naval Reserve. In December, 1920, he transferred to the Medical Corps, U. S. Navy and subsequently attained the rank of Rear Admiral to date from April 1, 1951.

During his naval career he served at many of the naval hospitals in the United States and on foreign shores. He served as the Medical Officer-in-Command of the Naval Hospitals, Coco Solo, C. Z.; Parris Island, S. C.; Houston, Tex.; and Philadelphia, Pa.

In August of 1935 he joined the *U. S. S. Louisville* and served until March, 1937, when he returned to the United States and was assigned to the Naval Hospital, Washington, D. C. In February of 1941 he was transferred to the U. S. Naval Hospital, Pearl Harbor, T. H., where he was serving when the Japanese attacked the Naval Base there on December 7, 1941.

He was a member of the American Medical Association and a Diplomate of the American Board of Internal Medicine, and had been a Fellow of the American College of Physicians since 1935.

Prepared by Bureau of Medicine and Surgery, Department of the Navy.

DR. EDWARD ANDREW PILLSBURY

Dr. Edward Andrew Pillsbury, of Frankenmuth, Michigan, died October 9, 1951, at the age of 74. He was one of a few remaining Associates of the College who were originally members of the American Congress on Internal Medicine and became Associates of the College when the Congress was absorbed in 1926.

Dr. Pillsbury had for many years been on the staff of St. Mary's Hospital in Saginaw, and on the Courtesy Staff of St. Joseph Hospital in Flint, and of the Saginaw General Hospital. He graduated from the University of Michigan Medical School in 1903, and had practiced General Medicine primarily with a special interest in Diseases of the Chest. He was a veteran of the Spanish-American War, and a charter member of the Frankenmuth State Hospital, of which he was a Director.

DR. EDGAR JONES

Edgar Jones, M.D., F.A.C.P., a gentle and quietly inspiring physician and scholar, died suddenly of coronary thrombosis in his office at Vanderbilt University Hospital in Nashville, Tenn., on October 27, 1951.

Dr. Jones can be said to have been a true product of the South and one of its leaders in medicine. Except for four years which he spent in postgraduate training and teaching in the North, he developed at Vanderbilt University School of Medicine into one of the South's foremost hematologists.

Born October 20, 1903, in Readyville, Tenn., Dr. Jones received his preparatory education in Nashville where in 1921 he entered the College of Arts and Sciences at Vanderbilt University. He continued his studies at Vanderbilt and in 1929 he was graduated from the School of Medicine. He spent the next year at the Lakeside Hospital in Cleveland, as an intern in medicine, and then returned to Vanderbilt University Hospital as Assistant Resident in Medicine on the service of Dr. C. Sidney Burwell. In the following year he obtained a Josiah Macy Fellowship to work at the University of Rochester Medical School in the Department of Medicine with Dr. William S. McCann. On the completion of this fellowship he was appointed Instructor in Medicine at Rochester. In 1934 he returned to the faculty of Vanderbilt University Medical School. At the time of his death he was Associate Professor of Medicine.

Dr. Jones was an able, well-rounded, versatile clinician and teacher, but his chief interest was in hematology. Gradually, in an unassuming fashion, he quietly became a recognized authority in hematology. His list of published papers dating from 1927, when he was a medical student, includes a variety of hematologic subjects in addition to other clinical observations. His recent investigations, which were conducted in association with Dr. William J. Darby, included studies of the fundamental nutritional aspects of the macrocytic anemias. Equally as impressive is the list of societies in which he held membership. In addition to the American College of Physicians, of which he became a Fellow in 1947, he was a member of the American Clinical and Climatological Association, the Association of American Physicians, the American Federation for Clinical Research, the Society for Experimental Biology and Medicine and the International Society of Hematology.

Above all, Dr. Jones will never be forgotten by his friends, his patients, and his colleagues for his complete readiness at any time to place himself unstintingly at their service. His relationships with people were warm and it is doubtful if he ever made an unkind or slurring remark about anyone. Absolutely regardless of personal inconvenience and without thought of personal gain, always good-humoredly helpful and constructively critical, never too busy when accosted by student or house-officer, to him truly the highest compliment can be paid: he was a physician's physician. To those who knew him his death is irreconcilable and the loss is irreplaceable.

F. Tremaine Billings, Jr., M.D., F.A.C.P.

PROGRAM

THE AMERICAN COLLEGE OF PHYSICIANS

Thirty-third Annual Session

CLEVELAND, OHIO

April 21–25, 1952

GENERAL SESSIONS AND SYMPOSIA

Maurice C. Pincoffs, Baltimore, Md., President

COMMITTEE ON ARRANGEMENTS

Roy W. Scott, General Chairman

Fay A. LeFevre, Assistant General Chairman

John D. Battle, Jr.
A. Carlton Ernstene
Joseph M. Hayman, Jr.
Charles S. Higley
Harry D. Piercy
John E. Rauschkolb
Walter M. Solomon

COMMITTEE ON AUDITORIUM

Walter M. Solomon, Chairman

Charles H. Brown
Stanley M. Goldhamer
Boyd G. King
Robert A. Reading
A. Benedict Schneider, Jr.
M. Irving Sparks

COMMITTEE ON HOSPITAL CLINICS

Joseph M. Hayman, Jr., Chairman

University Hospitals

Myron August ..... Lutheran Hospital
Harold G. Curtis ..... Sunny Acres Sanitarium
Curtis F. Garvin ..... Cleveland City Hospital
Gerald T. Kent ..... University Hospitals
Arthur D. Nichol ..... St. Luke's Hospital
Fred C. Oldenburg ..... St. Vincent Charity Hospital
Harry V. Paryzek ..... St. Alexis Hospital
Arthur J. Patek, Jr. ..... Mt. Sinai Hospital
William L. Proudfit ..... Cleveland Clinic Hospital
Harold Schwartz ..... Crile Veterans Administration Hospital
Sidney E. Wolpaw ..... Cleveland City Hospital

COMMITTEE ON HOTELS AND TRANSPORTATION

John E. Rauschkolb, Chairman

James R. Bell
Frank J. Doran
Morton L. Goldhamer
Samuel Hantman
Edward M. Kline

COMMITTEE ON ENTERTAINMENT

Harry D. Piercy, Chairman

William P. Garver
Joseph I. Goodman
Louis E. Lieder
Edward A. Marshall
E. Perry McCullagh
Robert M. Stecher

COMMITTEE ON PANEL DISCUSSIONS

A. Carlton Ernstene, Chairman

Edmund E. Beard
Harold Feil
Edward O. Harper
Charles F. McKhann
Arthur D. Nichol
Irvine H. Page

COMMITTEE ON PUBLICITY

Charles S. Higley, Chairman

Milton E. Bobey
Henry J. John
Richard S. Knowlton
Vernon C. Rowland

COMMITTEE ON TELEVISED CLINICS

John D. Battle, Jr., Chairman

Austin B. Chinn
Everett N. Collins
Iredell M. Hinnant
Helena Hoelscher
Thomas Kinney
Reginald Shipley
Edward E. Woldman

COMMITTEE ON LADIES' ENTERTAINMENT

Mrs. A. Carlton Ernstene, Chairman
Mrs. Charles S. Higley, Co-Chairman

Mrs. Harold Feil
Mrs. William P. Garver
Mrs. Henry J. John
Mrs. Fay A. LeFevre
Mrs. Charles F. McKhann
Mrs. Robert M. Stecher

HONORARY CO-OPERATING COMMITTEE

Torald H. Sollmann, Dean Emeritus, Western Reserve University School of Medicine
Joseph T. Wearn, Dean, Western Reserve University School of Medicine
Fred W. Dixon, President, Ohio State Medical Association
Francis Bayless, President, Cleveland Academy of Medicine
Edward L. Worthington, Director of Welfare, City of Cleveland
Fred G. Carter, Superintendent, St. Luke's Hospital
Stanley A. Ferguson, Superintendent, City Hospital
Sigmund L. Friedman, Director, Mt. Sinai Hospital
William B. Seymour, Director, University Hospitals
Sister M. Srancetta, Administrator, St. Vincent Charity Hospital
Clarence M. Taylor, Executive Director, The Cleveland Clinic Foundation

INVITATION

Cleveland and its fifty-seven suburbs in Cuyahoga County are honored at the opportunity to have as their guests the members of the American College of Physicians, and we hope to make this 33d Annual Session one to be long remembered both by the City and by the members of the College. Joining in this opportunity to entertain so

many distinguished guests is the Academy of Medicine of Cleveland with its 2,400 members, the Cleveland Medical Library Association, the Medical School of Western Reserve University, and the more than twenty hospitals which make Cleveland a great medical center.

Cleveland with its Public Hall, modern and spacious, its modern shopping center, its beautiful public mall and its atmosphere of cordiality will help to make your days downtown comfortable, enjoyable and worth while.

Many of you will find time between sessions at Public Hall to visit the medical center of Western Reserve University, the research and hospital facilities of the Cleveland Clinic, and many of the hospitals on both the east and west side of the city.

Those of you who visit such institutions on the east side as the University medical center, the Cleveland Clinic, St. Luke's Hospital, Huron Road Hospital and Mount Sinai Hospital will find adjacent to the campus of Western Reserve University the impressive Allen Memorial Library—the home of the Cleveland Medical Library Association, a branch of the Army Medical Library, and the offices of the Academy of Medicine, where also you will find the Howard Dittrick Museum of Historical Medicine.

You will also find it convenient on your way up or down town to stop into Cleveland's famous Museum of Health, the first of such institutions in this country. It is located at 8911 Euclid Avenue.

Downtown Cleveland will offer you an opportunity to observe clinical procedures at St. Vincent Charity Hospital, a few blocks from the downtown business center. The west side, easily reached by taxi or bus, is the home of Cleveland's City Hospital with its many units, St. John's Hospital, Lakewood Hospital and several others. You will find, if you visit these and other institutions, many new wings or buildings, and others in the course of construction or in blueprint form for development next year.

On the fringes of the County, but easily reached by taxi or public transportation, are the new Marymount Hospital on the south edge of the County, Sunny Acres Sanitarium, and the two Government Hospitals—Veterans Administration at Brecksville and Crile Hospital, also operated by the Veterans Administration. United States Public Health Service Hospital is easily visited on the way up the hill to Shaker Heights and St. Luke's Hospital.

Those of you who are interested in the problems of developing Civil Defense organizations in your community will find the headquarters of the medical section of Cleveland's Civil Defense organization in City Hall, just across Lakeside Avenue from the Public Auditorium. In the City Hall also you will find the office of the Commissioner of Health and his staff.

Space will not permit mention of all the other medical institutions in Cleveland, including the smaller hospitals and modern Health Stations of the City of Cleveland, all of which are worth visiting and all of whom join heartily in the hope that you will find time to get at least a quick glance at Cleveland's ability to develop research and to serve its population adequately and in a manner fitting the great progress of American Medicine.

GENERAL INFORMATION

GENERAL HEADQUARTERS

Cleveland Public Auditorium

Registration headquarters, the information bureau, technical exhibits, general sessions, morning symposia, panel discussions, clinical-pathological conferences, televised clinics, meetings of committees, of the Board of Regents and of the Board of Governors. The Annual Convocation will be held in the Music Hall of the Public Auditorium, and the Annual Banquet will take place in the Grand Ballroom of the Hotel Statler.

HOTEL ACCOMMODATIONS

A fully adequate number of hotel guest rooms has been reserved in fairly close proximity to the Public Auditorium, and a Housing Bureau, working through the Committee on Hotels and Transportation, has been set up at the Cleveland Convention Bureau, 511 Terminal Tower, Cleveland 13, Ohio. In view of the fact that the American Heart Association is meeting in Cleveland, April 17–19, and the American Board of Internal Medicine is giving one of its oral examinations at Cleveland also, April 17–19, a hotel reservation form has been devised for use of all three groups, thus preventing the necessity of having to move from one hotel to another between meetings. Applications for rooms should be made to the Housing Bureau, preferably on the official form provided by the College or by the American Heart Association or by the American Board of Internal Medicine, but in the absence of the form, the Housing Bureau will handle letters of application, provided the applicant identifies himself with the College and its Annual Session, or with one of the above organizations. It is requested that three choices of hotels be indicated and that a reasonable range of rates be shown. Whenever possible, arrangements should be made for occupancy of rooms accommodating two persons. Confirmation from the hotel where the reservation has been made will be mailed to each applicant. If after making reservations the applicant finds it is impossible to attend, he is requested to notify the Housing Bureau promptly, so that his accommodations may be made available to another physician.

LIST OF HOTELS

Hotel	For One Person	For Two Persons		Suites
		Double Bed	Twin Beds	
Alcazar	$6.50–$8.00	$8.50–$10.00	$8.50–$12.00	$12.00–$20.00
Allerton	4.00– 7.00 3.50 R.W.	6.50– 9.00	7.00– 10.00 5.50 R.W.	12.00– 20.00
Auditorium	4.00– 7.00	6.00– 9.00	8.50– 9.50	14.00– 20.00
Belmont	3.25– 3.50	5.00– 5.75	4.25– 6.25	
Bolton Square	3.50– 5.50	5.50– 7.00	6.00– 7.50	8.00– 25.00
Carter	4.00– 7.50	6.00– 10.00	8.00– 12.00	20.00– 40.00
Cleveland	4.50– 8.00	7.00– 10.00	10.00– 15.00	18.00– 30.00—2 rms. 32.00 & up—3 rms.
Commodore	6.00– 7.50	8.00– 10.00	8.50– 12.00	12.00– 20.00
Hollenden	4.00– 8.00	6.00– 12.00	8.00– 15.00	15.00– 22.00—2 rms. 26.00 & up—3 rms.
Lake Shore	5.00 & up	8.00 & up	8.00 & up	10.00 & up
Olmsted	3.75– 6.00	6.50– 9.00	7.50– 9.50	10.00– 15.00
Park Lane Villa	5.00	6.00	7.00– 8.00	
Quad Hall	3.00– 6.00		6.00– 10.00	10.00– 18.00
St. Regis	3.00– 4.00	5.00– 8.00	5.00– 8.00	8.00– 12.00
Sovereign	5.00– 6.00	6.00– 10.00	6.00– 12.00	
Statler	4.50– 9.00	7.50– 10.50	9.00– 14.00	18.00– 26.00
Stockbridge	3.00	5.00	6.00	
Tudor Arms	4.50 & up		7.00 & up	14.00 & up
Wade Park Manor	5.50 & up	7.50 & up	8.50 & up	10.00 & up
Westlake	5.00– 6.00	8.00– 9.00	9.00 & up	10.00– 15.00

(These rates are subject to change at any time. The list includes some residential hotels which may not have rooms available for conventions at all times.)

Who May Register—

(*a*) All members of the American College of Physicians in good standing for 1952.
(*b*) All newly elected members.
(*c*) Graduate medical students pursuing courses in local institutions of Cleveland, including residents in Cleveland hospitals, without registration fee, **upon presentation of matriculation cards or other evidence of registration at these institutions**; admission to exhibits, general sessions, morning symposia and TV clinics.
(*d*) Members of the staff, including interns, of the Cleveland Hospitals participating in the program, without registration fee, **upon presentation of proper identification**; admission to exhibits, general sessions, morning symposia and TV clinics (this does not include courtesy staff members).
(*e*) Bona fide hospital residents, regardless of their location in North America, without registration fee, **upon presentation of proper credentials from their hospitals**; admission to exhibits, general sessions, morning symposia, and other program features where facilities are adequate.
(*f*) Members of the Medical Corps of the Army, Navy, Public Health Service, Air Force and Veterans Administration, either of the United States or Canada, without registration fee, **upon presentation of proper credentials.**
(*g*) Qualified physicians who may wish to attend this Session as visitors, sponsored in advance by letter or in person by a member of the College; such physicians shall pay a registration fee of $25.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published) included within such fee.

The above regulations are essential because of the increasingly large attendance at the Annual Sessions of the College, and the necessity of accommodating members first.

Registration Bureau—While official registration will start on Monday morning, April 21, advance registration of members and exhibitors will be provided for on Sunday, April 20, from 2:30 P.M. to 5:00 P.M. The Registration Bureau, located in the Public Auditorium, will be open through the week from 8:45 A.M. to 5:30 P.M.

Registration Blanks for all Clinics, Panel Discussions and Clinical-Pathological Conferences will be enclosed with the final program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

Bulletin Board for special announcements will be located near the Registration Bureau at the Public Auditorium.

Transportation—Local transportation arrangements are in charge of the Committee on Hotels and Transportation, which will issue full information at the meeting.

The General Business Meeting of the College will be held from 2:00 P.M. to 2:40 P.M., Thursday, April 24, immediately preceding the afternoon scientific session. All Masters and Fellows of the College are urged to be present. There will be the election of Officers, Regents and Governors, the annual reports of the Secretary-General, Executive Secretary and Treasurer. The President-Elect, Dr. T. Grier Miller, Philadelphia, will be inducted into office.

BOARD AND COMMITTEE MEETINGS

All meetings will be held at the Regents' and Governors' Headquarters in the Public Auditorium. Special meetings will be announced and posted.

A Dinner Meeting of the Board of Regents and of the Board of Governors will be held at the Hotel Statler, Sunday, April 20, at 7:00 P.M.

Committee on Nominations

(At the call of the Chairman)

Committee on Credentials

Saturday, April 19, 10:00 A.M., Regents'-Governors' Room, North Hall, Public Auditorium

Committee on Fellowships and Awards

Sunday, April 20, 10:00 A.M., Executive Secretary's Office, Public Auditorium

Committee on Finance

Sunday, April 20, 11:15 A.M., Executive Secretary's Office, Public Auditorium

Joint Meeting: Board of Regents and Board of Governors

Sunday, April 20, 2:00 P.M., North Hall, Public Auditorium

Committee on Educational Policy and Advisory Committee on Postgraduate Courses

Monday, April 21, 10:00 A.M., Regents'-Governors' Room, North Hall, Public Auditorium

Committee on Public Relations

Monday, April 21, 11:00 A.M., Regents'-Governors' Room, North Hall, Public Auditorium

Committee on the Annals of Internal Medicine

Monday, April 21, 12:00 M., Regents'-Governors' Room, North Hall, Public Auditorium

Inspection, Committee on Technical Exhibits

Monday, April 21, 10:30 A.M., starting from the Executive Secretary's Office, Public Auditorium

Meeting, Technical Exhibitors

Monday, April 21, 5:20 P.M., Room 3, North Hall, Public Auditorium

Board of Regents

*Tuesday, April 22, 12:00 M., Regents'-Governors' Room, North Hall, Public Auditorium

Board of Governors

*Wednesday, April 23, 12:00 M., Regents'-Governors' Room, North Hall, Public Auditorium

Annual Business Meeting

Thursday, April 24, 2:00 P.M., Music Hall, Public Auditorium

Board of Regents

*Friday, April 25, 12:00 M., Regents'-Governors' Room, North Hall, Public Auditorium

SPECIAL FEATURES

"The Mark Twain" Post-Convention Cruise—Arrangements have been consummated for a cruise down the Ohio River, Tennessee River and to the Kentucky Lake, one of the TVA "Great Lakes of the South." The *Delta Queen,* the cruise steamer, sets a new standard of luxury in river transportation. Lounging and observation rooms are comfortably and pleasantly appointed, and wide decks invite one to exercise or to rest. An orchestra will provide music for dancing. The dining room has a distinctly southern cuisine, and the hostess will provide a program of entertainment that is interesting and lots of fun. Additionally there will be daily, optional scientific motion picture programs, including "The Hypertensive Crises," "Problems of Rheumatoid Arthritis," the "Therapeutic Use of ACTH in Human Disease," "Management of the Failing Heart," "Allergy—Immunology and Treatment," the "Role of Gastroscopy in the Diagnosis and Treatment of Gastric Pathology" and "Urinary Infections—Bacteriology-Pathology and Treatment."

Members of the cruise will leave Cleveland at 11:30 P.M., Friday, April 25, board the ship at Cincinnati early Saturday morning, sail on the *Delta Queen* at 8:30 A.M., following the paths of LaSalle, Joliet, George Rogers Clark, Daniel Boone, the Singing Baptists, Mark Twain. All day, Sunday, cruise the lower Ohio River, and arriving Monday at Kentucky Dam, passing through the highest single lift lock on the American Continent into Kentucky Lake. After a forty mile cruise, return back to the Tennessee River. Tuesday, shore tour of Evansville and plant of Mead Johnson and Company; afternoon cruise the Ox-Bow bends; Wednesday, cruising the lower Ohio, with an afternoon tour of one of the distilleries at Louisville, tour of the City, Churchill Downs; Thursday, stop at Madison, Ind., visiting Clifty Falls State Park and Lanier Mansion; arrive Cincinnati, Friday, in ample time for early morning departures to all points by train or by air.

Inclusive prices range from $121.00, without bath, to a top of $184.25. Cruise under the direction of Mr. Leon V. Arnold, Travel Consultant, 36 Washington Square West, New York 11, N. Y., to whom requests should be sent for prospectus, deck plans, reservations, etc.

Concert, Orpheus Male Chorus, Monday, April 21, 8:45 P.M., Music Hall, Public Auditorium—The Committee on Entertainment is gratified to announce this Concert by the prize-winning chorus of America, under the direction of Dr. Charles D. Dawe, its founder and only conductor. For a quarter of a century this Chorus has maintained a record of artistic achievements unequalled in male chorus history. Not only is it the first and only American male chorus to win top honors in European competition, but in its every appearance in competition both abroad and in the United States it has won first prize. It boasts a repertoire as unusual as it is ample and varied, for it contains many works, dedicated to Dr. Dawe and the Chorus, which it has given a first performance and others given only by this group because of their exacting vocal and technical demands.

The Chorus has demonstrated its versatility by the high standard of its radio broadcasts, particularly those to and from Europe, for which it has received praise from the National and British Broadcasting Companies, and by its Victor recordings, which are used extensively by radio stations throughout the Country.

An additional feature of the program, in which the Committee takes pride in arranging, will be the appearance of Jerome Gross, M.D., a member of the Cleveland

* Buffet luncheon served.

Academy of Medicine, and also a member of a prominent family of physicians of Cleveland. Dr. Gross is an accomplished violinist, has appeared in numerous solo violin recitals in Cleveland, New York, Chicago and other cities. He has been soloist with the Cleveland Summer Symphony Orchestra and the Cleveland Philharmonic Orchestra in performances of the Tschaikovsky, Mendelssohn, and Conus concertos, and the Lalo Symphonie Espagnole. He has also participated in many chamber music programs, and is an ardent devotee of this type of music.

Admission to this Concert is free to all members and duly registered guests, and to the exhibitors at this Annual Session. However, for identification, show your registration badge (physicians, ladies or exhibitors).

The Annual Convocation and the President's Reception, Wednesday, April 23—The Annual Convocation of the College will be held at 8:30 P.M., April 23, in the Music Hall of the Public Auditorium. All members of the College and their families, and those of the public who are interested, are cordially invited. No tickets are required. All physicians elected Fellows of the College since the 1951 Convocation, and all previously elected Fellows who have not been formally inducted, should be present. Officers, Regents and Governors, and new Fellows to be inducted, are requested to assemble on the Third Floor Foyer of the Music Hall at 7:45 P.M., preparatory to the formation of the procession.

The Convocation ceremony will include the President's Address and the Convocational Oration, "The Administrative Process and Health Problems," by Raymond B. Allen, M.D., F.A.C.P., Director of the Psychological Strategy Board, Washington, D. C. The John Phillips Memorial Medal for 1952, the James D. Bruce Memorial Medal for 1952 and the Alfred Stengel Diploma for 1952 will be awarded. Recipients of Research Fellowships and of Latin-American Fellowships of the College for 1952 will be announced, and a Mastership will be conferred upon a distinguished member of the College. The class of new Fellows will be inducted by the President.

Following the Convocation, the President's Reception will be held in the Grand Ballroom of the Hotel Statler, followed by the Dance.

THE ANNUAL BANQUET, Thursday, April 24, 8:00 P.M.—The Annual Banquet will be held in the Ballroom of the Hotel Statler. A gala occasion, with excellent food, good fellowship and fine entertainment is assured. Dr. Abba Hillel Silver, for more than three decades spiritual leader of The Temple in Cleveland, eminent author, an authority on world affairs and an outstanding and brilliant speaker, will be the Speaker of the Day. Table reservations for groups may be arranged. **Tickets should be procured at the Registration Bureau in the Public Auditorium by 5:00 P.M., Wednesday, in order that adequate preparations may be concluded by the Committee.**

Specialized Cardiac Demonstration—The Program Committee has concluded arrangements for a Specialized Cardiac Demonstration daily in the North Hall of the Public Auditorium by J. Scott Butterworth, M.D., F.A.C.P., Associate Professor of Medicine, New York University—Bellevue Medical Center, New York, N. Y. The demonstration has considerable teaching value of a postgraduate nature. Three electron cardioscopes, each with a sixteen-inch screen, and three independent tapes will be run simultaneously, so that the listener may have his choice of a variety of conditions.

ENTERTAINMENT OF VISITING WOMEN

The Ladies' Committee looks forward with genuine pleasure to meeting the wives of the visiting members of the American College of Physicians, and cordially welcomes them to Cleveland.

Headquarters for registration, information, purchase of tickets, reservations for entertainments, and all other women's activities, will be on the mezzanine floor of the Hotel Statler. The Committee sincerely hopes the visiting wives will enjoy every minute of their stay in Cleveland.

Daily Program

9:00 A.M. to 4:00 P.M. Every day **Registration** at the Hotel Statler.

Monday, April 21

3:00 P.M. to 5:00 P.M. Tea and Reception at the Union Club to meet and welcome the Visitors, given by the Ladies' Committee.

8:00 P.M. Concert by the Orpheus Male Chorus of Cleveland. Music Hall, Public Auditorium. Admission by registration badge.

Tuesday, April 22

12:30 P.M. Luncheon and Fashion Show at the Carter Hotel Rainbow Room. Capacity, 500 guests. Tickets, $3.00.

As an added feature, one of Cleveland's favorite florists will demonstrate new and uncommon flower arrangements for a variety of occasions.

Wednesday, April 23

10:00 A.M. A sight-seeing tour of Cleveland's Cultural Gardens, Museums, Universities, Music Centers, and lovely homes—given through the courtesy of National Dairy Products Corporation, Processors of Sealtest Dairy Products—stopping at the Country Club for those desiring luncheon.

12:30 P.M. Luncheon at the Country Club, where busses will wait to return the guests (along an interesting route) to the hotel. Luncheon Tickets, $2.75.

A special attraction at the Luncheon will be the reading of his own poems by Mr. Joseph Newman, well-known Cleveland author, playwright, master of wit and a matchless raconteur.

(Luncheon accommodations are limited to 175. An early advance reservation is therefore desirable.)

2:30 P.M. A musical, "Travesty," composed and directed by the Women's Discussion Group of the Council on World Affairs, will be presented at Higbee's auditorium. Our visitors are cordially invited to attend this amusing skit. Tea will follow.

8:30 P.M. Annual Convocation of the College, Music Hall, Public Auditorium.

10:30 P.M. President's Reception and Dance, Grand Ballroom, Hotel Statler.

Thursday, April 24

Several entertainments available in Cleveland during the convention week have been selected and will be listed at the Information Desk. From this schedule, we hope our guests will choose a personally agreeable subject of interest. On the list will be: current plays at the theaters, the Symphony Concert program, show of the month at the Art Museum, Health Museum exhibits, a list of antique shops, Museum of Natural History displays, sports events, and other special features.

Tickets, when needed, may be procured at the Information Desk.

8:00 P.M. Annual Banquet of the College, Grand Ballroom, Hotel Statler.

For some who may not wish to attend the College Banquet, the Ladies' Committee has been able to secure a limited number of tickets for the Symphony Concert (Beethoven Ninth Symphony), under the direction of George Szell, at the Music Hall. For tickets, inquire at the Ladies' Registration Desk.

Color Televised Clinics—Through the courtesy of Smith, Kline & French Laboratories, Philadelphia, and the co-operation of the Columbia Broadcasting System

the College will present for the third year an interesting program of clinics televised in color from the Cleveland Clinic Hospital to the Public Auditorium in Cleveland, 9:00 A.M. to 10:50 A.M., daily, Tuesday through Friday. Color television is no longer an innovation in medical education, but has become a well established medium of medical teaching. Since the introduction of color television by Smith, Kline & French at the American Medical Association's meeting at Atlantic City in 1949, over 200,000 medical men have viewed these programs.

Supplementary Showing of "Medical Films That Teach"—The Medical Film Guild, of New York City, will show a wide variety of colored sound films of particular interest to members of the College in its projection room adjacent to their exhibit booth No. 18, on the main exhibit floor. Consult Mr. Joseph Hackel, President of the Medical Film Guild, at its booth concerning special films you desire to view, and he will schedule them at your convenience, if possible.

The Medical Film Guild is also providing the films constituting the scientific program for the Mark Twain Post-Convention Cruise.

The Technical Exhibit—The Technical Exhibit is located in the main exhibit hall of the Public Auditorium, and will be one of the finest and all-inclusive exhibits yet conducted by the College. The Committee on Exhibits maintains the highest possible standards in the conduct of this exhibit. Exhibitors are admitted only by invitation; irrelevant exhibits are eliminated, and only firms which present a group of approved products of scientific interest to the internist and allied specialist may exhibit.

Members and guests of the College are encouraged to accord the exhibitors courteous and interested attention. Many thousand dollars are expended by the exhibitors to bring to this College superior displays and up-to-date information concerning pharmaceuticals, equipment, medical books and medical services. The Technical Exhibitors gauge this meeting by the amount of interest shown and the co-operation displayed by the College. At no other meeting is there assembled a group of technical exhibits and technical exhibitors comparable as a whole to these at the meeting of the American College of Physicians.

Exhibits will be open from 8:45 A.M. to 5:30 P.M., daily, from Monday through Thursday, and from 8:45 A.M. to 2:30 P.M. on Friday. Physicians are urged to use the intermissions in the program for inspection of the exhibits, but these intermissions are inadequate for a thorough visit and inspection of the large number of exhibits, and, thus, physicians are encouraged to spend some additional time in this important part of the meeting.

LIST OF TECHNICAL EXHIBITORS

	Booth
Abbott Laboratories, North Chicago, Ill.	97–98
American Hospital Supply Corporation, Evanston, Ill.	20–21
American Journal of Medicine, Inc., The, New York, N. Y.	79
Ames Company, Inc., Elkhart, Ind.	43
Appel Medical Sculptures, Doris, Lynn, Mass.	10
Appleton-Century-Crofts, Inc., New York, N. Y.	40
Armour Laboratories, The, Chicago, Ill.	122–123
Association of American University Presses, New York, N. Y.	96
Ayerst, McKenna & Harrison Limited, New York, N. Y.	82
Baum Co., Inc., W. A., New York, N. Y.	88
Becton, Dickinson & Co., Rutherford, N. J.	118–119
Bilhuber-Knoll Corp., Orange, N. J.	76
Bischoff Company, Inc., Ernst, Ivoryton, Conn.	13
Blakiston Company, The, Philadelphia, Pa.	19
Brewer & Company, Inc., Worcester, Mass.	31

	Booth
Bristol Laboratories Inc., New York, N. Y.	37–38
Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N. Y.	8
Burton, Parsons & Co., Inc., Washington, D. C.	41
Cambridge Instrument Co., Inc., New York, N. Y.	61
Chilcott Laboratories—The Maltine Company, Morris Plains, N. J.	130–131
Ciba Pharmaceutical Products, Inc., Summit, N. J.	99–100
Clersite Company, Chicago, Ill.	23
Collins, Inc., Warren E., Boston, Mass.	110
Commercial Solvents Corporation, New York, N. Y.	67–68
Davies, Rose & Company, Limited, Boston, Mass.	4
Davis Company, F. A., Philadelphia, Pa.	7
Devereux Schools, Devon, Pa., and Santa Barbara, Calif.	53
DeVilbiss Company, The, Toledo, Ohio	58
Doak Company, Inc., Cleveland, Ohio	102
Doho Chemical Corporation, New York, N. Y.	85–86
Dome Chemicals Inc., New York, N. Y.	127
Edin Company, Inc., Worcester, Mass.	6
Electro-Physical Laboratories, Inc., Stamford, Conn.	84
Fischer & Co., H. G., Franklin Park, Ill.	120
Fleet Co., Inc., C. B., Lynchburg, Va.	121
Flint, Eaton & Company, Decatur, Ill.	91
Geigy Pharmaceuticals, New York, N. Y.	63
General Electric Co., X-Ray Department, Milwaukee, Wis.	2–3
Gerber Products Company, Fremont, Mich.	74
Grune & Stratton, Inc., New York, N. Y.	54
Harrower Laboratory, Inc., The, Jersey City, N. J., and St. Louis, Mo.	33
Heinz Company, H. J., Pittsburgh, Pa.	95
Hoeber, Inc., Paul B., New York, N. Y.	49
Hoffman-La Roche, Inc., Nutley, N. J.	115
Hollister-Stier Laboratories, Wilkinsburg, Pa., Spokane, Wash., and Los Angeles, Calif.	51
Irwin, Neisler & Company, Decatur, Ill.	112–113
Jones Metabolism Equipment Co., Chicago, Ill.	42
LaMotte Chemical Products Company, Towson, Baltimore, Md.	92
Lea & Febiger, Philadelphia, Pa.	50
Lederle Laboratories Division, American Cyanamid Company, New York, N. Y.	34–35–36
Lilly and Company, Eli, Indianapolis, Ind.	105–106–107
Lippincott Company, J. B., Philadelphia, Pa.	9
Macmillan Company, The, New York, N. Y.	111
Massengill Company, The S. E., Bristol, Tenn.	135
McNeil Laboratories, Inc., Philadelphia, Pa.	75
Mead Johnson & Company, Evansville, Ind.	116
Medco Products Company, Tulsa, Okla.	45

	Booth
Medical Bureau, The, Chicago, Ill.	48
Medical Film Guild, Ltd., New York, N. Y.	18
Merck & Co., Inc., Rahway, N. J.	77–78
Merrell Company, The Wm. S., Cincinnati, Ohio	5
Miller Surgical Company, Chicago, Ill.	32
Mosby Company, The C. V., St. Louis, Mo.	62
National Drug Company, The, Philadelphia, Pa.	66
Nepera Chemical Co., Inc., Yonkers, N. Y.	134
Oxford University Press, Inc., New York, N. Y.	83
Parke, Davis & Company, Detroit, Mich.	14–15–16–17
Pfizer & Co., Inc., Chas., Brooklyn, N. Y.	47
Picker X-Ray Corporation, White Plains, N. Y.	64–65
Riker Laboratories, Inc., Los Angeles, Calif.	46
Robins Company, Inc., A. H., Richmond, Va.	133
Rystan Company, Inc., Mount Vernon, N. Y.	108
Sanborn Company, Cambridge, Mass.	72–73
Sandoz Chemical Works, Inc., New York, N. Y.	69
Saranac Lake Medical Facilities, Inc., Saranac Lake, N. Y.	136
Saunders Company, W. B., Philadelphia, Pa.	59–60
Schenley Laboratories, Inc., Lawrenceburg, Ind.	87
Schering Corporation, Bloomfield, N. J.	101
Schieffelin & Co., New York, N. Y.	124
Searle & Co., G. D., Chicago, Ill.	132
Sharp & Dohme, Inc., Philadelphia, Pa.	70–71
Smith, Kline & French Laboratories, Philadelphia, Pa.	55–56
Squibb & Sons, E. R., New York, N. Y.	103–104
Stethetron Sales Company, Wenonah, N. J.	114
Swift & Company, Chicago, Ill.	109
Taylor Instrument Companies, Rochester, N. Y.	11–12
Technicon Cardiograph Corp., New York, N. Y.	117
Travenol Laboratories, Inc., Morton Grove, Ill.	39
U. S. Vitamin Corporation, New York, N. Y.	137
Upjohn Company, The, Kalamazoo, Mich.	80–81
Vanpelt & Brown, Inc., Richmond, Va.	1
Varick Pharmacal Co., Inc., New York, N. Y.	125–126
Wallace & Tiernan Products, Inc., Belleville, N. J.	22
Warren-Teed Products Company, The, Columbus, Ohio	52
White Laboratories, Inc., Kenilworth, N. J.	93
Williams & Wilkins Company, The, Baltimore, Md.	57
Winthrop-Stearns Inc., New York, N. Y.	89–90
Woodward Medical Personnel Bureau, Chicago, Ill.	44
Wyeth Incorporated, Philadelphia, Pa.	94
Year Book Publishers, Inc., The, Chicago, Ill.	120

OUTLINE OF THE CLEVELAND SESSION

Bold Type indicates events at Public Auditorium

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	April 21	April 22	April 23	April 24	April 25
9:00 A.M. to 11:00 A.M.	Morning free. **Registration, Exhibits, etc.**	Hospital Clinics **Color Televised Clinics**	**Morning Symposia* Color Televised Clinics**	Hospital Clinics **Color Televised Clinics**	**Morning Symposia* Color Televised Clinics**
11:30 A.M. to 12:45 P.M.		**4 Panel Discussions C-P Conferences**	**4 Panel Discussions C-P Conferences**	**4 Panel Discussions C-P Conferences**	**4 Panel Discussions C-P Conferences**
2:00 P.M. to 5:00 P.M.	**1st General Session**	**2nd General Session**	**3rd General Session**	**Annual Business Meeting 4th General Session**	**5th General Session**
Evening	**Concert Orpheus Male Chorus**		7:45 **Pre-Convocation Assembly** 8:30 **Convocation** 10:15 President's Reception and Ball	8:00 Banquet	

* Two simultaneous Series.

GENERAL SESSIONS PROGRAM

Music Hall, Public Auditorium

FIRST GENERAL SESSION

Monday Afternoon, April 21, 1952

Presiding Officer
ROY W. SCOTT, F.A.C.P., Cleveland, General Chairman

P.M.

2:00 **Addresses of Welcome:**
The Honorable THOMAS A. BURKE, Mayor of the City of Cleveland.
JOHN S. MILLIS, Ph.D., LL.D., President, Western Reserve University.
FRANCIS BAYLESS, M.D., President, The Cleveland Academy of Medicine.

Response to Addresses of Welcome:
MAURICE C. PINCOFFS, M.A.C.P., President, The American College of Physicians.

Presiding Officer
President MAURICE C. PINCOFFS, M.A.C.P., Baltimore

2:30 **The James D. Bruce Memorial Lecture on Preventive Medicine: Immunity to Poliomyelitis.**
JAMES H. S. GEAR, M.D. (by invitation), Deputy Director, The South African Institute for Medical Research, Johannesburg.

3:10 **Histoplasmosis.**
AMOS CHRISTIE, M.D. (by invitation), Professor of Pediatrics, Vanderbilt University School of Medicine.

3:30 INTERMISSION.

3:45 **The Present Status of Ballistocardiography.**
ISAAC STARR, M.D. (by invitation), Hartzell Research Professor of Therapeutics, University of Pennsylvania School of Medicine.

4:05 **The Physiology of Congenital Heart Disease.**
RICHARD J. BING, M.D. (by invitation), Professor of Experimental Medicine, The Medical College of Alabama.

4:25 **Prognosis Following the Blalock-Taussig Operation: An Analysis of One Thousand Cases.**
HELEN B. TAUSSIG, M.D. (by invitation), Associate Professor of Pediatrics, Johns Hopkins University School of Medicine.

4:45 **The Surgical Repair of Interatrial Septal Defects.**
CHARLES P. BAILEY, F.A.C.S. (by invitation), Professor and Head of the Department of Thoracic Surgery, Hahnemann Medical College and Hospital of Philadelphia.

5:05 ADJOURNMENT.

SECOND GENERAL SESSION

Music Hall, Public Auditorium

Tuesday Afternoon, April 22, 1952

Presiding Officer

DAVID P. BARR, F.A.C.P., New York

P.M.

2:00 **Angiocardiography in Mediastinal and Pulmonary Disease.**
CHARLES T. DOTTER, M.D. (by invitation), Assistant Professor of Radiology, Cornell University Medical College.

2:20 **Osteoporosis and Osteomalacia.**
I. SNAPPER, M.D. (by invitation), Director of Medical Education, Mount Sinai Hospital, New York City.

2:40 **The Role of Sodium Studies in the Therapy of Cirrhosis.**
WILLIAM J. EISENMENGER, M.D. (by invitation), Hospital of the Rockefeller Institute for Medical Research.

3:00 **Latent Steatorrhea.**
DOUGLAS G. CAMERON (Associate), Assistant Professor of Medicine, McGill University Faculty of Medicine.

3:20 INTERMISSION.

3:40 **Observations on the Splenic Flexure Syndrome.**
THOMAS E. MACHELLA, F.A.C.P., Assistant Professor of Medicine, University of Pennsylvania School of Medicine.

3:55 **Acute Pericarditis in Adults of Middle Age.**
WILLIAM HALL LEWIS, JR., F.A.C.P., New York City.

4:10 **Cat Scratch Disease.**
WORTH B. DANIELS, F.A.C.P., Professor of Clinical Medicine, Georgetown University School of Medicine.

4:25 **Diagnosis and Management of Asymptomatic Isolated Intrathoracic Nodules.**
SIDNEY E. WOLPAW, F.A.C.P., Assistant Clinical Professor of Medicine, Western Reserve University School of Medicine.

4:40 **Treatment of Hypertension with Oral Protoveratrine.**
SIBLEY W. HOOBLER, F.A.C.P., Assistant Professor of Internal Medicine, University of Michigan Medical School.

4:55 ADJOURNMENT.

THIRD GENERAL SESSION

Music Hall, Public Auditorium

Wednesday Afternoon, April 23, 1952

Presiding Officer

HUGH J. MORGAN, F.A.C.P., Nashville

P.M.

2:00 **The John Phillips Memorial Lecture: A Discussion of the Concept of Cardiac Failure in the Light of Recent Physiologic Studies in Man.**
ANDRÉ F. COURNAND, M.D. (by invitation), Professor of Medicine, Columbia University College of Physicians and Surgeons.

2:40 **The Evaluation of Anticoagulant Therapy in Congestive Heart Failure Using Depo-Heparin, Dicumarol and Tromexan.**
GEORGE C. GRIFFITH, F.A.C.P., Professor of Medicine, University of Southern California School of Medicine.

3:00 **Electrolytes and Congestive Failure.**
T. S. DANOWSKI, F.A.C.P., Renziehausen Professor of Research Medicine, University of Pittsburgh School of Medicine.

3:20 INTERMISSION.

3:40 **The Physiology of the External Pancreatic Secretion in Man.**
JOHN M. HOWARD, Captain, (MC), AUS (by invitation), Army Medical Service Graduate School, Washington.

3:55 **Abnormal Bleeding Associated with Blood Transfusion.**
J. GARROTT ALLEN, M.D. (by invitation), Professor of Surgery, University of Chicago School of Medicine.

4:10 **Factors Influencing Recovery from Radiation Injury.**
LEON O. JACOBSON, F.A.C.P., Associate Dean, Division of Biological Sciences, and Professor of Medicine, University of Chicago School of Medicine.

4:25 **Immunologic Mechanisms in Idiopathic Thrombocytopenic Purpura.**
WILLIAM J. HARRINGTON, M.D. (by invitation), Instructor in Medicine, Washington University School of Medicine.

4:40 **Indications and Contraindications for the Treatment of Thyroid Cancer with Radioactive Iodine.**
WILLIAM H. BEIERWALTES (Associate), Assistant Professor of Internal Medicine, University of Michigan Medical School.

4:55 ADJOURNMENT.

ANNUAL CONVOCATION

Wednesday Evening, April 23, 1952

8:30 O'Clock

Music Hall, Public Auditorium

LEMUEL C. MCGEE, Marshal

Pre-Convocation Assembly of Fellows to be inducted, Officers, Regents and Governors, at 7:45 P.M., Balcony Foyer, Music Hall, Public Auditorium.

All members of the profession and the general public are cordially invited. No admission tickets required.

1. Processional.
2. The President's Address:
   MAURICE C. PINCOFFS.
3. Conferring of Fellowships by the President.
4. Conferring of Mastership by the President.
5. Presentation of the John Phillips Memorial Medal for 1952.
6. Presentation of the James D. Bruce Memorial Medal for 1952.
7. Presentation of the Alfred Stengel Memorial Award for 1952.
8. Announcement of Research Fellows for 1952–1953.
9. Announcement of Latin-American Fellows for 1951–1952.

10. Convocational Oration: "The Administrative Process and Health Problems." RAYMOND B. ALLEN, F.A.C.P., Director, Psychological Strategy Board.
11. Recessional.

President's Reception

The President's Reception and Dance will follow at 10:30 o'clock in the Grand Ballroom of the Hotel Statler. A cordial invitation is extended to all members and guests, with their families.

FOURTH GENERAL SESSION

Music Hall, Public Auditorium

Thursday Afternoon, April 24, 1952

P.M.

2:00 THE ANNUAL BUSINESS MEETING.

All Fellows and Masters are urged to be present and to participate more actively in the administrative problems of the College. Reports will be received from the Secretary-General, Executive Secretary and Treasurer; elections of new Officers, Regents and Governors will take place; President-Elect T. Grier Miller, of Philadelphia, Pa., will be inducted as President and make a brief inaugural address.

2:40 INTERMISSION.

Presiding Officer

CHARLES A. DOAN, F.A.C.P., Columbus

3:00 Prognosis in Psychosomatic Disease.
HENRY W. BROSIN, F.A.C.P., Professor of Psychiatry and Chairman, Department of Psychiatry, University of Pittsburgh School of Medicine.

3:20 Evaluation of Developments in the Surgical Treatment of Pulmonary Tuberculosis.
J. BURNS AMBERSON, F.A.C.P., Professor of Medicine, Columbia University College of Physicians and Surgeons; Visiting Physician in Charge, Chest Service, Bellevue Hospital (Columbia University Division).

3:40 The Application of Cytological Diagnosis in Cancer of the Stomach, Pancreas and Biliary System.
HENRY M. LEMON, M.D. (by invitation), Assistant Professor of Medicine, Boston University School of Medicine.

4:00 Dietary Modification of the Metabolic and Clinical Effects of ACTH and Cortisone.
LAURANCE W. KINSELL, F.A.C.P., Director, Institute for Metabolic Research, Highland-Alameda County Hospital, Oakland, Calif.

4:20 The Use of Cortisone and ACTH in Idiopathic Thrombocytopenic Purpura and in Acquired Hemolytic Anemia.
MURIEL MEYERS, M.D. (by invitation), Assistant Professor of Internal Medicine, University of Michigan Medical School; Research Assistant, Thomas Henry Simpson Memorial Institute for Medical Research.

4:40 **Changes in Connective Tissue Reaction Induced by Cortisone.**
ROBERT H. EBERT, M.D. (by invitation), Markle Foundation Scholar, and Assistant Professor of Medicine, University of Chicago School of Medicine.

5:00 ADJOURNMENT.

Thursday Evening, April 24, 1952

8:00 O'Clock

Grand Ballroom, Hotel Statler

THE ANNUAL BANQUET OF THE COLLEGE

(Procure tickets at the Registration Bureau, Public Auditorium, before 5:00 P.M., Wednesday. Arrangements may be made for table reservations, if desired.)

Consult Special Banquet Program

Toastmaster:

ROY W. SCOTT, F.A.C.P., Cleveland

Address of the Day:

"AMERICAN LEADERSHIP IN THE WORLD TODAY"

RABBI ABBA HILLEL SILVER, Cleveland

FIFTH GENERAL SESSION

Music Hall, Public Auditorium

Friday Afternoon, April 25, 1952

Presiding Officer

CYRUS C. STURGIS, F.A.C.P., Ann Arbor

P.M.

2:00 **Thyroiditis.**
GEORGE CRILE, JR., F.A.C.S. (by invitation), Cleveland Clinic Foundation.

2:20 **Clinical Results of Aortic-Sinus Graft Operation in Arteriosclerotic Heart Disease.**
HAROLD FEIL, F.A.C.P., Clinical Professor of Medicine, Western Reserve University School of Medicine.

2:40 **Antimicrobial Therapy in Pulmonary and Extrapulmonary Tuberculosis.**
H. CORWIN HINSHAW, F.A.C.P., Clinical Professor of Medicine, Stanford University School of Medicine.

3:00 **The Disturbance of the Normal Bacterial Ecology by the Administration of Antibiotics with the Development of New Clinical Syndromes.**
DAVID T. SMITH, F.A.C.P., Professor of Bacteriology and Associate Professor of Medicine, Duke University School of Medicine.

3:20 INTERMISSION.

3:40 **The Emotional Problems of High Blood Pressure.**
EDWARD WEISS, F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine.

4:00 **The Neurosurgical Treatment of Spontaneous Intracerebral Hemorrhage Simulating the Common Stroke.**
MICHAEL SCOTT, F.A.C.S. (by invitation), Clinical Professor and Head of Department of Neurosurgery, Temple University School of Medicine.

4:20 **Rehabilitation of the Hemiplegic.**
DONALD A. COVALT, M.D. (by invitation), Associate Professor of Physical Medicine and Rehabilitation, New York University College of Medicine.

4:40 **The Protean Clinical Features of Leptospirosis and Its Diagnosis.**
JOHN A. HIGHTOWER, Captain, (MC), USA (by invitation), Army Medical Research and Graduate School and University of Maryland School of Medicine.

5:00 ADJOURNMENT.

MORNING SYMPOSIA

In the place of the Morning Lectures there are presented this year four Symposia, two of which will be held on Wednesday morning and two on Friday morning. In each instance basic physiologic principles will be discussed by the first speaker and clinical aspects by the other participants.

Attendance at these Symposia is open to all members and guests of the College. **Admission by regular registration badge; no special tickets.**

Wednesday, April 23, 1952

I. SYMPOSIUM ON THYROID DISEASE

Music Hall, Public Auditorium

Presiding Officer

MARION A. BLANKENHORN, F.A.C.P., Cincinnati

A.M.

9:00 **The Thyroid and Its Endocrine Relationships.**
JAMES HOWARD MEANS, F.A.C.P., Jackson Professor of Clinical Medicine (Emeritus), Harvard Medical School; Physician, Massachusetts Institute of Technology; Board of Consultation, Massachusetts General Hospital.

9:50 INTERMISSION.

10:00 **Hyperthyroidism: An Evaluation of Anti-Thyroid Drugs Followed by Subtotal Thyroidectomy.**
ELMER C. BARTELS, F.A.C.P., Lahey Clinic, Boston.

10:20 **Hyperthyroidism: Long Term Treatment with Anti-Thyroid Drugs.**
SAMUEL P. ASPER, M.D. (by invitation), Assistant Professor of Medicine, Johns Hopkins University School of Medicine.

10:40 **Hyperthyroidism: Treatment with Radioactive Iodine.**
E. PERRY MCCULLAGH, F.A.C.P., Cleveland Clinic.

11:00 ADJOURNMENT.

II. SYMPOSIUM ON ARTERIAL HYPERTENSION

Little Theater, Public Auditorium

Presiding Officer

JOHN MINOR, F.A.C.P., Washington

A.M.

9:00 **Some Aspects of the Pathogenesis of Essential Hypertension.**
EPHRAIM SHORR, M.D. (by invitation), Associate Professor of Medicine, Cornell University Medical College.

9:50 INTERMISSION.

10:00 **New Drug Therapies in Arterial Hypertension.**
ROBERT W. WILKINS, F.A.C.P., Associate Professor of Medicine, Boston University School of Medicine; Chief, Hypertension Clinic, Massachusetts Memorial Hospitals.

10:20 **Psychogenic Influences in Hypertension.**
EUGENE B. FERRIS, JR., F.A.C.P., Professor of Medicine, University of Cincinnati College of Medicine.

10:40 **The Role of the Adrenal in Arterial Hypertension.**
JOHN P. MERRILL (Associate), Instructor in Medicine, Harvard Medical School.

11:00 ADJOURNMENT.

Friday, April 25, 1952

III. SYMPOSIUM ON DIABETES

Music Hall, Public Auditorium

Presiding Officer

JOSEPH M. HAYMAN, JR., F.A.C.P., Cleveland

A.M.

9:00 **Endocrine Regulation of the Blood Sugar.**
JEROME W. CONN, F.A.C.P., Professor of Internal Medicine, University of Michigan Medical School.

9:40 INTERMISSION.

9:50 **Basic Principles in the Therapy of Diabetes.**
HENRY T. RICKETTS, F.A.C.P., Professor of Medicine, University of Chicago School of Medicine.

10:10 **Diabetic Acidosis as a Therapeutic Problem.**
GARFIELD G. DUNCAN, F.A.C.P., Clinical Professor of Medicine, Jefferson Medical College of Philadelphia.

10:30 **The Kimmelstiel-Wilson Syndrome.**
STANTON L. EVERSOLE, M.D. (by invitation), Instructor in Pathology, Johns Hopkins University School of Medicine.

10:45 **Diabetic Retinopathy.**
BERNARD BECKER, M.D. (by invitation), Instructor in Ophthalmology and Mellon Fellow in Ophthalmology, Wilmer Institute, Johns Hopkins University School of Medicine.

11:00 ADJOURNMENT.

IV. SYMPOSIUM ON RHEUMATIC FEVER

Little Theater, Public Auditorium

Presiding Officer

HAROLD H. JONES, F.A.C.P., Winfield, Kans.

A.M.

9:00 The Natural History of Rheumatic Fever.
EDWARD F. BLAND, F.A.C.P., Physician, Massachusetts General Hospital.

9:50 INTERMISSION.

10:00 Recent Developments in the Prevention of Rheumatic Fever.
HAROLD B. HOUSER, Major, (MC), AUS (by invitation), Streptococcal Diseases Laboratory, Warren Air Force Base, Wyoming.

10:20 Present Status of Diagnostic Tests for Rheumatic Fever.
MACLYN MCCARTY, M.D. (by invitation), Hospital of the Rockefeller Institute for Medical Research.

10:40 The Use of Cortisone and ACTH in Rheumatic Fever.
JOSEPH J. BUNIM, F.A.C.P., Associate Professor of Medicine, New York University College of Medicine.

11:00 ADJOURNMENT.

PANEL DISCUSSIONS

and

CLINICAL-PATHOLOGICAL CONFERENCES

Topics of intimate interest and practical value to all members of the profession have been chosen. Qualified men have been selected as leaders and members of the panel personnel. All panels are scheduled from Tuesday through Friday, 11:30 A.M. to 12:45 P.M., and will be held at the Public Auditorium.

In place of one regular panel discussion, the Program Committee is offering a clinical-pathological conference each day at which the clinical protocol of an interesting medical case will be discussed by the participants who are expected to make the correct diagnosis. The post-mortem findings will then be presented by the pathologist in whose department the case was autopsied. Moderators and conference personnel will then answer questions that may arise as time permits. The clinical protocols of the four cases to be presented appear in a separate booklet to be sent with the program, so that members may have the opportunity of making their own diagnosis before the formal conference.

Applications for tickets to all Panels (the C-P Conferences will be held in the Music Hall which has practically unlimited seating, and will not require tickets) may be made in advance by members on a regular application form which will accompany the program. Tickets will also be available at the Registration Bureau, Public Auditorium. NON-MEMBERS may not register by mail, but should secure their tickets directly at the meeting.

Applicants may submit in writing three weeks before the Session, through the Executive Secretary of the College, any questions concerning any phase of the subjects listed. Moderators and panel personnel will answer those questions which they feel are applicable to the subject under discussion, and will answer as many questions as time permits.

PANEL DISCUSSIONS

	Little Theater (Adjoining Music Hall) Public Auditorium (Admission by ticket only)	Room 1 South Hall Public Auditorium (Admission by ticket only)	Room 2 North Hall (West) Public Auditorium (Admission by ticket only)	Room 3 North Hall (East) Public Auditorium (Admission by ticket only)	Music Hall Public Auditorium (Admission by badge; no tickets)
Capacity	675	300	500	575	3,000
Tuesday April 22 11:30 A.M. to 12:45 P.M.	**I** **The Mechanism of Congestive Heart Failure** Moderator *Herrman L. Blumgart Boston *Thomas J. Dry Rochester, Minn. *George C. Griffith Los Angeles *Robert L. McMillan Winston-Salem *Eugene A. Stead, Jr. Durham *Carl J. Wiggers Cleveland	**II** **Blood Transfusion, Plasma and Plasma Substitutes** Moderator *Elmer L. DeGowin Iowa City Henry K. Beecher Boston I. S. Ravdin Philadelphia James V. Warren Atlanta *Lawrence E. Young Rochester, N. Y.	**III** **Diagnosis and Treatment of Pancreatitis** Moderator *Henry L. Bockus Philadelphia *M. W. Comfort Rochester, Minn. Robert Elman St. Louis *Albert M. Snell Palo Alto J. Earl Thomas Philadelphia	**IV** **Management of the Psychoneurotic Patient** Moderator *William C. Menninger Topeka *Kenneth E. Appel Philadelphia Douglas D. Bond Cleveland *Henry W. Brosin Pittsburgh *John Minor Washington *Hugh J. Morgan Nashville	**V** **Clinical-Pathological Conference** Moderator *Roy W. Scott Cleveland *Howard B. Sprague Boston *Johnson McGuire Cincinnati *Chester S. Keefer Boston Alan R. Moritz Cleveland
Introduced by:	*A. Carlton Ernstene Cleveland	*Harry V. Paryzek Cleveland	*Fred C. Oldenburg Cleveland	*Edward O. Harper Cleveland	

*F.A.C.P.

PANEL DISCUSSIONS—*Continued*

	Little Theater (Adjoining Music Hall) Public Auditorium (Admission by ticket only)	Room 1 South Hall Public Auditorium (Admission by ticket only)	Room 2 North Hall (West) Public Auditorium (Admission by ticket only)	Room 3 North Hall (East) Public Auditorium (Admission by ticket only)	Music Hall Public Auditorium (Admission by badge; no tickets)
Capacity	675	300	500	575	3,000
Wednesday April 23 11:30 A.M. to 12:45 P.M.	**VI** **Functional Pathology of the Liver**	**VII** **Management of Diabetes Mellitus and Its Complications**	**VIII** **Electrolyte and Fluid Exchange**	**IX** **Diagnosis and Treatment of Peripheral Arterial Disease**	**X** **Clinical-Pathological Conference**
	Moderator *Cecil J. Watson Minneapolis	Moderator *Garfield G. Duncan Philadelphia	Moderator Daniel Darrow New Haven	Moderator *Edgar A. Hines, Jr. Rochester, Minn.	Moderator *Albert M. Snell Palo Alto
	Arthur J. Patek, Jr. Cleveland *Hans Popper Chicago *Leon Schiff Cincinnati *Dwight L. Wilbur San Francisco	*Alexander Marble Boston *Edward H. Mason Montreal * E. Perry McCullagh Cleveland *Thomas P. Sharkey Dayton	Robert W. Berliner Bethesda A. C. Corcoran Cleveland *T. S. Danowski Pittsburgh *Robert F. Pitts New York	Geza DeTakats Chicago John B. Hazard Cleveland *Hugh Montgomery Philadelphia *Irving S. Wright New York	*Hugh J. Morgan Nashville *Herrman L. Blumgart Boston *Eugene A. Stead, Jr. Durham Lawrence J. McCormack Cleveland
Introduced by:	*Edward A. Marshall Cleveland	R. W. Schneider Cleveland	*Charles S. Higley Cleveland	*Fay A. LeFevre Cleveland	

* F.A.C.P.

PANEL DISCUSSIONS—*Continued*

	Little Theater (Adjoining Music Hall) Public Auditorium (Admission by ticket only)	Room 1 South Hall Public Auditorium (Admission by ticket only)	Room 2 North Hall (West) Public Auditorium (Admission by ticket only)	Room 3 North Hall (East) Public Auditorium (Admission by ticket only)	Music Hall Public Auditorium (Admission by badge; no tickets)	Ballroom, 4th Floor Public Auditorium (Use elevator) (Admission by badge; no tickets)
Capacity	675	300	500	575	3,000	1,000
Thursday April 24 11:30 A.M. to 12:45 P.M.	**XI** **Newer Concepts of Pulmonary Physiology**	**XII** **Obesity and Its Consequences**	**XIII** **Hormonal and Chemotherapy of Cancer**	**XIV** **Pathogenesis and Treatment of Hypertension**	**XV** **Clinical-Pathological Conference**	**XVI** **Theoretic Electrocardiography**
	Moderator *Julius H. Comroe, Jr. Philadelphia	Moderator *Edward H. Rynearson Rochester, Minn.	Moderator *C. P. Rhoads New York	Moderator *Irvine H. Page Cleveland	Moderator *Hugh J. Morgan Nashville	Moderator *George E. Burch, Jr. New Orleans
	N. L. Kaltreider Rochester, N. Y. *D. W. Richards, Jr. New York Richard L. Riley Baltimore George W. Wright Trudeau	*Edmund E. Beard Cleveland Brunhilde Bruch New York *Frank A. Evans Pittsburgh R. Gordon Gould, Ph.D. Los Alamos	*Charles A. Doan Columbus Charles B. Huggins Chicago John H. Lazzari Cleveland *Willard O. Thompson Chicago	*Eugene B. Ferris, Jr. Cincinnati George A. Perera New York *Edward Weiss Philadelphia *Robert W. Wilkins Boston	*Cyrus C. Sturgis Ann Arbor *Cecil J. Watson Minneapolis *David P. Barr New York Thomas Kinney Cleveland	Robert P. Grant Baltimore *Franklin D. Johnston Ann Arbor *Louis N. Katz Chicago *Calvin F. Kay Philadelphia
Introduced by:	*Myron August Cleveland	*E. Perry McCullagh Cleveland	*Boyd G. King Cleveland	*Curtis F. Garvin Cleveland		*Harold Feil Cleveland

*F.A.C.P.

PANEL DISCUSSIONS—*Continued*

	Little Theater (Adjoining Music Hall) Public Auditorium (Admission by ticket only)	Room 1 South Hall Public Auditorium (Admission by ticket only)	Room 2 North Hall (West) Public Auditorium (Admission by ticket only)	Room 3 North Hall (East) Public Auditorium (Admission by ticket only)	Music Hall Public Auditorium (Admission by badge; no tickets)
Capacity	675	300	500	575	3,000
Friday April 25 11:30 A.M. to 12:45 P.M.	**XVII** **Electrocardiography**	**XVIII** **Treatment of Uremia**	**XIX** **Treatment of the Anemias**	**XX** **Management of Peptic Ulcer and Its Complications**	**XXI** **Clinical-Pathological Conference**
	Moderator *George E. Burch, Jr. New Orleans	Moderator *Joseph R. Elkinton Philadelphia	Moderator *Cyrus C. Sturgis Ann Arbor	Moderator *Walter L. Palmer Chicago	Moderator *William S. Middleton Madison
	*Franklin D. Johnston Ann Arbor *Louis N. Katz Chicago *Maurice Sokolow San Francisco *Charles C. Wolferth Philadelphia	*Joseph M. Hayman, Jr. Cleveland W. J. Kolff Cleveland *Robert F. Loeb New York John P. Merrill Boston	*William Dameshek Boston *Willis M. Fowler Iowa City *Thomas Hale Ham Cleveland *Richard W. Vilter Cincinnati	*Theodore L. Althausen San Francisco *Austin B. Chinn Cleveland *Lester A. Dragstedt Chicago *Julian M. Ruffin Durham	*William H. Bunn Youngstown *Charles A. Doan Columbus *Dwight L. Wilbur San Francisco Thomas Kinney Cleveland
Introduced by:	*Harold Feil Cleveland	*Edward M. Kline Cleveland	*Stanley M. Goldhamer Cleveland	*Everett N. Collins Cleveland	

*F.A.C.P.

THE CLINIC SESSIONS

Color Television of Medical Clinics

The following series of clinics will be televised in color on Tuesday, Wednesday, Thursday and Friday mornings between 9:00 A.M. and 10:50 A.M. from the Cleveland Clinic Hospital to the Public Auditorium by a group of physicians from the participating hospitals and medical schools.

Due to changing programs from one clinic to another, a slight lag will occur. However, it is believed that the times indicated will be approximately correct.

Admission by regular badge; no special tickets required.

Tuesday, April 22, 1952

9:00– 9:20 Peripheral Vascular Disease.
FIORINDO A. SIMEONE, M.D. (by invitation), Professor of Surgery (City Hospital), Western Reserve University, Cleveland; and IRVING S. WRIGHT, F.A.C.P., Clinical Professor of Medicine, Cornell University Medical College, New York City.

9:25– 9:35 Intra-arterial Blood Transfusion.
DONALD E. HALE, M.D. (by invitation), Head of the Department of Anesthesiology, Cleveland Clinic.

9:40– 9:50 Solitary Pulmonary Lesions.
SIDNEY E. WOLPAW, F.A.C.P., Assistant Clinical Professor of Medicine (Mt. Sinai Hospital), Western Reserve University; and HARVEY J. MENDELSOHN, M.D. (by invitation), Assistant Professor of Surgery (Thoracic), Western Reserve University.

9:55–10:10 Methods of Skin Testing in Allergic Disease.
WILLIAM P. GARVER, F.A.C.P., Clinical Instructor in Medicine (City Hospital), Western Reserve University; and MYRON A. WEITZ, M.D. (by invitation), Head of the Department of Allergy, Mt. Sinai Hospital, Cleveland.

10:15–10:30 Hormone Treatment of Metastatic Breast Cancer.
E. PERRY MCCULLAGH, F.A.C.P., Head of the Department of Endocrinology, Cleveland Clinic.

10:35–10:50 The "L.E." Test.
JOHN R. HASERICK (Associate), Department of Dermatology, Cleveland Clinic.

Wednesday, April 23, 1952

9:00– 9:20 The Jaundiced Patient.
ARTHUR J. PATEK, JR., M.D. (by invitation), Professor of Medicine (Mt. Sinai Hospital), Western Reserve University; and CECIL J. WATSON, F.A.C.P., Professor of Medicine, University of Minnesota Medical School.

9:25– 9:40 Congenital Heart Disease Amenable to Surgery.
HAROLD FEIL, F.A.C.P., Clinical Professor of Medicine, Western Reserve University; and HERMAN K. HELLERSTEIN, M.D. (by invitation), Clinical Instructor in Medicine, Western Reserve University.

9:45– 9:55 Dermatologic Lesions of Medical Interest.
CURTIS F. GARVIN, F.A.C.P., Assistant Clinical Professor of Medicine, Western Reserve University.

10:00–10:15 **Ophthalmopathy.**
BROWN M. DOBYNS, M.D. (by invitation), Associate Professor of Surgery (City Hospital), Western Reserve University.

10:20–10:30 **The Shoulder-Hand Syndrome.**
HAROLD SCHWARTZ (Associate), Chief, Cardiology Department, Crile Veterans Administration Hospital, Cleveland.

10:35–10:50 **Demonstration of Neurological Cases.**
LOUIS J. KARNOSH, M.D. (by invitation), Head of the Department of Neuropsychiatry, Cleveland Clinic, and Clinical Professor of Nervous Diseases, Western Reserve University.

Thursday, April 24, 1952

9:00– 9:20 **Hereditary Hemolytic Disease.**
RUSSELL L. HADEN, F.A.C.P., Consultant in Medicine and Research, Cleveland Clinic; and THOMAS HALE HAM, F.A.C.P., Professor of Medicine, Western Reserve University.

9:25– 9:35 **Measurement of Pulmonary Function; Chronic Emphysema.**
SCOTT R. INKLEY, M.D. (by invitation), Instructor in Medicine, Western Reserve University; and JULIUS H. COMROE, JR., F.A.C.P., Professor of Physiology and Pharmacology, University of Pennsylvania Graduate School of Medicine.

9:40– 9:55 **Rehabilitation of the Hemiplegic.**
KEITH KEELER, M.D. (by invitation), Assistant Professor of Physical Medicine and Rehabilitation, Western Reserve University.

10:00–10:15 **X-Ray-Pathology Conference on Gastro-intestinal Lesions.**
RAFAEL DOMINGUEZ, M.D. (by invitation), Pathologist, St. Luke's Hospital; Assistant Professor of Pathology, Western Reserve University; and DONALD BRANNAN, M.D. (by invitation), Department of Röentgenology, St. Luke's Hospital, Cleveland.

10:20–10:30 **Cardiac Output and Blood Volume Measured by Radioactive Iodinated Albumin.**
WALTER H. PRITCHARD, M.D. (by invitation), Assistant Professor of Medicine, Western Reserve University; and W. JAMES MACINTYRE, Ph.D. (by invitation), Physicist-in-Charge, Atomic Energy Committee, Western Reserve University.

10:35–10:50 **Syndromes Due to Adreno-Cortical Hyperactivity.**
SAMUEL SPECTOR, M.D. (by invitation), Assistant Professor of Pediatrics, Western Reserve University.

Friday, April 25, 1952

9:00– 9:20 **Cardiac-Pathology Conference: Unusual Forms of Heart Disease.**
A. CARLTON ERNSTENE, F.A.C.P., Chief of Staff, Medical Division, Cleveland Clinic; and ALAN R. MORITZ, M.D. (by invitation), Professor of Pathology, Western Reserve University.

9:25– 9:40 **Treatment of Acute Ulcerative Colitis.**
WALTER L. PALMER, F.A.C.P., Professor of Medicine, University of Chicago School of Medicine; and GEORGE CRILE, JR., M.D. (by invitation), Department of Surgery, Cleveland Clinic.

9:45–10:00 **Treatment of Severe Bronchial Asthma; Effect of ACTH and Cortisone in Allergic Disease.**
MCKINLEY LONDON, F.A.C.P., Chief of the Department of Allergy, St. Luke's Hospital, Cleveland; and LOUIS E. LIEDER, F.A.C.P., Area Consultant in Allergy, Veterans Administration; Visiting Physician in Allergy, Mt. Sinai Hospital, Cleveland.

10:05–10:15 Acute Leukemia.
ROBERT W. HEINLE, M.D. (by invitation), Associate Professor of Medicine, Western Reserve University.

10:20–10:30 Selection of Patients for Mitral Commissurotomy.
GEORGE H. A. CLOWES, M.D. (by invitation), Senior Instructor in Surgery (City Hospital); and SALVATORE M. SANCETTA (Associate), Instructor in Medicine (City Hospital), Western Reserve University.

10:35–10:50 Hodgkin's Disease.
U. V. PORTMANN, M.D. (by invitation), Head of the Department of Therapeutic Radiology; and JOHN B. HAZARD, M.D. (by invitation), Head of the Department of Pathology, Cleveland Clinic.

THE CLINIC SESSIONS

Clinics at Hospitals

The regular Hospital Clinics will be conducted on Tuesday and Thursday from 9:00 A.M. to 10:30 or 11:00 A.M., whereas Morning Symposia will be conducted on Wednesday and Friday mornings, thus eliminating competition between these features of the program.

Admission to the Hospital Clinics will require special tickets, which will be issued to MEMBERS in advance of the Session and to NON-MEMBERS directly at the Registration Bureau in the Public Auditorium. Application forms for tickets for the Hospital Clinics and Panel Discussions will be sent to all members with the program.

The Committee on Panels is committed to a program of clinics in the true sense of that term—that is, patients will be shown and discussed, rather than having presentations of formal short papers. A wide range of medical topics important to the clinician is offered. Visitors will have the opportunity to see patients at close range and to observe hospital methods in Cleveland.

All clinics must terminate promptly at the designated hour, in order that members may have adequate time to reach the Panel Discussions, which start at 11:30 A.M.

The Committee on Transportation recommends the use of taxicabs for reaching the Hospital Clinics, and will arrange that there shall be an adequate number of taxicabs available also for the return trip.

Tickets will be required for each and every one of the Hospital Clinics, unless specifically otherwise mentioned. The co-operation of every one in securing his clinic tickets will assist greatly in distributing the attendance according to the capacity of each meeting room. It is self-evident that a clinic arranged for fifty will lose its value for all if a hundred are present. Ticket registration, naturally, is the only effective method of keeping the attendance within the capacities indicated.

Member registration blanks for the clinics should be filled out and returned to the Executive Secretary promptly. Upon receipt by the College Office, proper tickets will be selected and held at the Registration Bureau in the Public Auditorium, or, on the request of the member, will be mailed to him. Reservations by mail cannot be made after April 5, but reservations may be made in person at the Registration Bureau on the afternoon preceding any clinic day, providing tickets are still available.

Members who reserve Clinic Tickets are urgently requested to notify the Executive Secretary, and to return their tickets, if they find they will be unable to attend.

PROGRAM OF HOSPITAL CLINICS

Tuesday, April 22, 1952

A — CLEVELAND CITY HOSPITAL

(3395 Scranton Road)

Pathology Amphitheater

(Capacity, 150)

9:00 The Management of Malignant Hypertension.
Maurice Sokolow, San Francisco.

9:30 Heart Disease and the Aging Process.
Hugh J. Morgan, Nashville.

10:00 Recess.

10:10 Lipedema and Physiologic Edema.
Edgar A. Hines, Jr., Rochester, Minn.

10:30 The Macrocytic Anemias.
Cyrus C. Sturgis, Ann Arbor.

B-1 — CLEVELAND CLINIC

(Euclid Avenue at 93rd Street)

Fourth Floor Auditorium, North Building

(Capacity, 200)

9:00 Disseminated Lupus Erythematosus.
John R. Haserick.

9:20 Ulcerative Colitis.
Everett N. Collins.

9:40 Hyperparathyroidism.
Robert W. Schneider.

10:00 Recess.

10:20 Treatment of Coronary Disease.
Herrman L. Blumgart, Boston.

10:40 Aphasia.
Louis J. Karnosh.

B-2 — CLEVELAND CLINIC

(Euclid Avenue at 93rd Street)

Founder's and Staff Room

(Capacity, 125)

9:00 Multiple Myeloma.
Russell L. Haden.

9:20 Hypertension.
Robert D. Taylor.

9:40 Treatment of Adrenal Insufficiency.
E. Perry McCullagh.

10:00 Recess.

10:20 Problems Related to Hepatitis.
Albert M. Snell, Palo Alto.

10:40 Liver Biopsy.
H. R. Rossmiller.

C

MT. SINAI HOSPITAL

(1800 E. 105th Street)

Pathology Amphitheater

(Capacity, 70)

9:00 Leukemia.
Stanley M. Goldhamer.

9:20 Anemia of Folic Acid Deficiency.
Benjamin B. Teitelbaum.

9:40 Recess.

10:00 Gout.
Alexander B. Gutman, New York.

10:20 Subarachnoid Hemorrhage.
Julius Wolkin.

10:40 Group Therapy for Obese Diabetics.
Joseph I. Goodman.

D

ST. LUKE'S HOSPITAL

(11311 Shaker Blvd.)

Prentiss Auditorium

(Capacity, 250)

9:00 Polycythemia Vera.
Charles A. Doan, Columbus.

9:30 Urethane in Leukemia and Myeloma.
Charles S. Higley.

9:50 Late Complications of Diabetes.
M. Irving Sparks.

10:10 Dermatological Manifestations of Lymphomas.
Herbert H. Johnson.

10:30 Clinical Aspects of Lymphomas.
Ovid O. Meyer, Madison.

E ST. VINCENT CHARITY HOSPITAL

(S.E. Cor. Central Avenue and E. 22nd Street)

Auditorium, Nurses' Home

(Capacity, 200)

9:15 Selection of Cases for Mitral Valve Surgery.
Henry A. Zimmerman.

9:45 Surgical Aspects of Mitral Stenosis.
Earle B. Kay.

10:15 Recess.

10:30 Familial Aspects of Congenital Heart Disease.
Frank R. Hanrahan.

10:50 Prognostic Aspects of Congenital Heart Disease.
Bradley Hull.

11:10 Hemodynamics of Carotid Artery Ligation of Aneurysm of Cerebral Circulation.
Spencer Braden and Keith Sheldon.

F-1 UNIVERSITY HOSPITALS

(2065 Adelbert Road)

Lakeside Amphitheater

(Capacity, 166)

9:00 A Problem in the Lymphoma Group.
William S. Middleton, Madison.

9:20 Preliminary Pain in Myocardial Infarction.
Harold Feil.

9:40 Recess.

10:00 Hemolytic Anemia.
Thomas Hale Ham.

10:20 Management of Psychosomatic Patients.
Douglas D. Bond.

10:40 Management of Lower Nephron Nephrosis.
Max Miller.

F-2 UNIVERSITY HOSPITALS

MacDonald House Amphitheater

(Capacity, 100)

9:00 Brucellosis.
Wesley W. Spink, Minneapolis.

9:20 Myxedema with Ascites.
Wm. McK. Jefferies.

9:40 Recess.

10:00 Mitral Commissurotomy.
Walter H. Pritchard.

10:20 Multiple Sclerosis.
Clark T. Randt.

10:40 Multiple Myeloma.
Gordon C. Meacham.

HOSPITAL CLINICS

Thursday, April 24, 1952

A

CLEVELAND CITY HOSPITAL

(3395 Scranton Road)

Pathology Amphitheater

(Capacity, 150)

9:00 Disseminated Lupus Erythematosus.
William S. Middleton, Madison.
9:30 Clinical and Laboratory Observations on Patients Before and After Commissurotomy.
Salvatore M. Sancetta and George H. A. Clowes.
10:00 Recess.
10:10 Blood Dyscrasias.
Charles A. Doan, Columbus.
10:30 The Use of I-131 in the Diagnosis of Thyroid Tumors.
Brown M. Dobyns.

B-1

CLEVELAND CLINIC

(Euclid Avenue at 93rd Street)

Fourth Floor Auditorium, North Building

(Capacity, 200)

9:00 Hypertension.
Irvine H. Page.
9:20 Peripheral Arterial Disease.
Fay A. LeFevre.
9:40 Treatment of Anuria and Uremia.
W. J. Kolff.
10:00 Recess.
10:20 Treatment of Bleeding Peptic Ulcer.
Walter L. Palmer, Chicago.
10:40 Subdural Hematoma.
Robert D. Mercer.

B-2

CLEVELAND CLINIC

(Euclid Avenue at 93rd Street)

Founder's and Staff Room

(Capacity, 125)

9:00 Complications and Sequelae of Myocardial Infarction.
A. Carlton Ernstene.
9:20 Beryllium Poisoning.
H. Scott VanOrdstrand.
9:40 Lung Biopsy in Diffuse Pulmonary Lesions.
Donald B. Effler.
10:00 Recess.

10:20 Hyperinsulinism.
E. H. Rynearson, Rochester, Minn.
10:40 Physiology of Cor Pulmonale.
Richard N. Westcott.

C

MT. SINAI HOSPITAL

(1800 E. 105th Street)

Pathology Amphitheater

(Capacity, 70)

9:00 Disseminated Lupus.
Samuel Hantman.
9:20 Coronary Artery Disease.
Mortimer L. Siegel.
9:40 Recess.
10:00 Bleeding Peptic Ulcer.
Leon Schiff, Cincinnati.
10:20 Intractable Peptic Ulcer.
Erwin Levin.
10:40 Psychiatric Emergencies.
Oscar B. Markey.

D

ST. LUKE'S HOSPITAL

(11311 Shaker Blvd.)

Prentiss Auditorium

(Capacity, 250)

9:00 Effect of Exchange Resins on Edema.
Arthur D. Nichol.
9:20 Regional Enteritis.
Burrill B. Crohn, New York.
9:50 Colitis with Adrenal Dysfunction.
Edward E. Woldman.
10:10 Adrenal Dysfunction.
Edmund E. Beard.
10:30 Endocrines and Nutrition.
Elmer L. Sevringhaus, Nutley, N. J.

E

ST. VINCENT CHARITY HOSPITAL

(S.E. Cor. Central Avenue and E. 22nd Street)

Auditorium, Nurses' Home

(Capacity, 200)

9:15 Use of N.P.H. in Diabetes Mellitus.
M. Irving Sparks.
9:35 Case of Libman-Sacks Disease with Five Years Remission.
Charles S. Stone.

9:55 Management of Coronary Thrombosis with and without Anticoagulants.
John P. Anderson.

10:25 Recess.

10:40 Interesting X-Ray Studies of Peptic Ulcer.
Emmett J. O'Malley.

11:00 Results of Surgical Treatment of Chronic Arthritis and Other Joint Deformities.
Robert M. Stecher and Joseph Edmund Brown.

F-1

UNIVERSITY HOSPITALS

(2065 Adelbert Road)

Lakeside Amphitheater

(Capacity, 166)

9:00 Bacterial Pneumonia.
Marion A. Blankenhorn, Cincinnati.

9:20 Paroxysmal Cold Hemoglobinuria.
W. S. Jordan.

9:40 Recess.

10:00 Hypertension.
John C. Leonard, Hartford.

10:20 Disseminated Lupus.
Austin Weisberger.

10:40 Constitution and Diabetes.
John L. Caughey.

F-2

UNIVERSITY HOSPITALS

MacDonald House Amphitheater

(Capacity, 100)

9:00 Diabetes.
Garfield G. Duncan, Philadelphia.

9:20 Fructose in Diabetic Coma.
James W. Craig.

9:40 Recess.

10:00 Upper Respiratory Infection.
John Dingle.

10:20 Pernicious Anemia.
Robert W. Heinle.

10:40 Eczema.
Herbert H. Johnson.

CLEVELAND POST-CONVENTION "MARK TWAIN CRUISE"

THE *Delta Queen*, a fine river steamer, leaves Cincinnati for the Post-Convention "Mark Twain Cruise" at 9:00 a.m. Saturday, April 26. Breakfast will be served on the steamer. The Cruise will terminate at Cincinnati on the morning of May 2, in ample time to make all morning train and air connections. The six days will be filled with rest, comfort, relaxation, enjoyment, good fellowship, and a professional program to complete the agenda of the Annual Meeting of the College.

Cruise members will leave Cleveland on Friday evening, April 25, at 11:50, New York Central Lines, and reach Cincinnati at 7:10 the following morning. Pullman reservations should be made with your other train reservations. Pullman is not included in the price. Members from the West and South will make Cleveland their destination and so get the advantage of the round trip fare without additional cost for the return via Cincinnati. Members from the East and North will make Cincinnati their destination, going via Cleveland and returning via Cincinnati, and so get the advantage of a round trip fare. The departure from Cincinnati makes ticketing very simple and economical for all.

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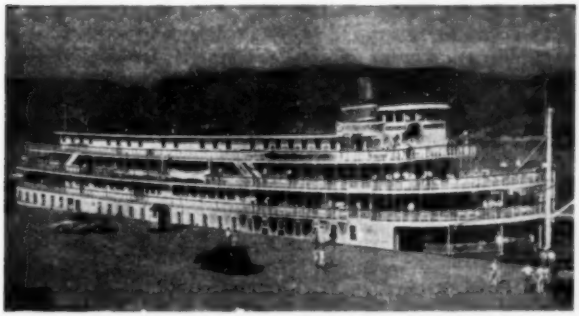

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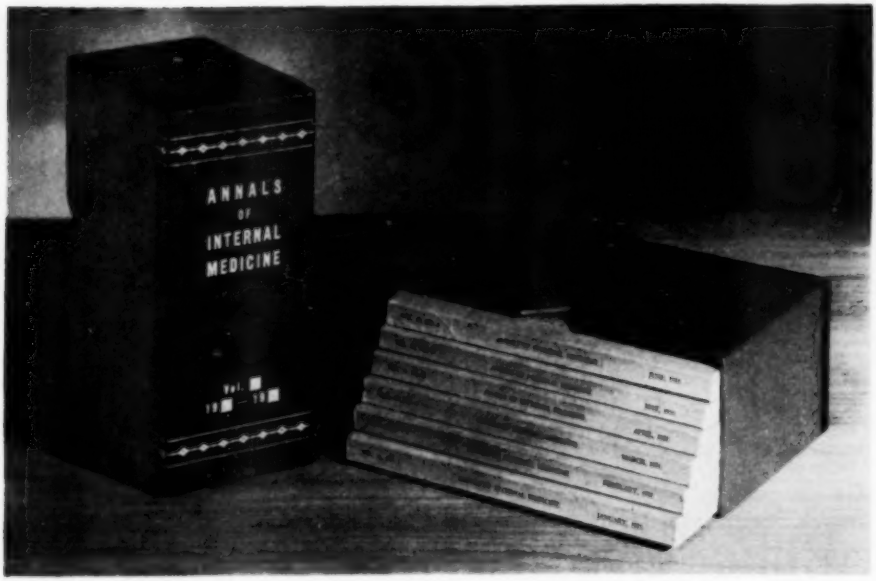

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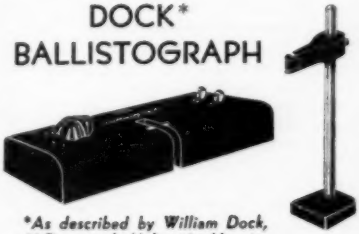

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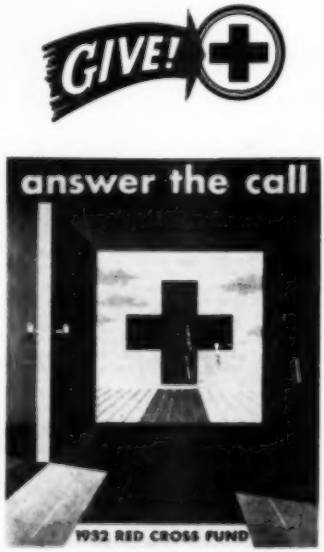

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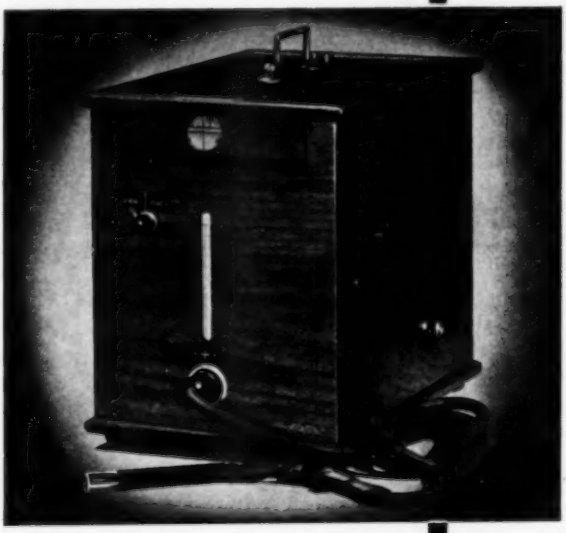

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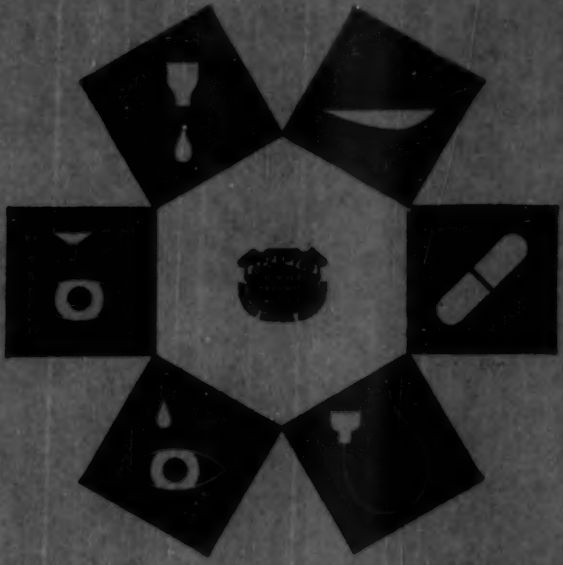

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